

STUDIES ON RENAL FUNCTION

THE EFFECT OF INHALATION OF CARBON DIOXIDE ON RENAL
CLEARANCES IN NORMALS, IN ESSENTIAL HYPERTENSION
AND IN VARIOUS KIDNEY DISORDERS.

BY

BERTIL HOOD.

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BERTIL HOOD

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FROM THE MEDICAL DEPARTMENT OF FALUN (HEAD: DR. A. ENGEL)

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ESSELTE AKTIEBOLAG

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Preface.

My best thanks are due to Drs H. W. Smith, W. Goldring and H. Chasis and to Drs I. H. Page and A. C. Corcoran for the hospitality they showed me during my stay in the United States two years ago and to Dr A. Engel, my clinical teacher, for his great interest and help and for affording good working facilities.

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The shortcomings and limitations of the present study are very apparent. Studies such as the maximal tubular excretory capacity, saturation limit and extraction ratio under the action of the agent used for influencing the renal function would probably have been of interest but had to be omitted owing to local conditions. It seems easy to conceive of a number of control studies that would have been useful, such as studies during hyperventilation. Such were planned but could not be executed on account of the departure abroad of the trained technician.

Falun, April 10th, 1949

BERTIL HOOD.

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CHAPTER I.

REVIEW OF LITERATURE.

Anatomy of Normal Renal Circulation.

In the case of the mammalian kidney Bowman (1842) concluded that, to reach the tubules, all the blood must traverse the glomeruli to be then distributed from the efferent glomerular arterioles. This concept was challenged by Ludwig, who showed that some interlobular arteries terminated directly in the peritubular capillary plexus, a finding that has been repeatedly confirmed. Ludwig (1871) then showed that from some of the afferent arterioles there is given off a small branch which communicates directly with the capillary plexus. For this branch the name Ludwig's arteriole has become established.

Further, the possibility remains that the capsular blood supply, which is derived from the interlobular arteries, the capsular artery as well as from extra-renal sources, can deliver significant amounts of blood via the capsulo-cortical connections into the cortical capillary bed.

Among the cortico-medullary vascular connections, the arteriolae rectae, Ludwig distinguished between those which according to the structure of their walls and their origin were real arteries and those which were the non-muscular stretched-out efferent vessels of the glomeruli adjacent to the medullary border.

The existence of these various paths of non-glomerular vascular supply has been repeatedly confirmed. There remains the important question to what extent these pathways occur in the normal, the aging and the diseased kidney, their frequency and size having a definite bearing on how closely the quantitative excretory studies can picture the underlying anatomical conditions.

Mc Callum (1939) pointed out that the formation of the non-glomerular vessels always depends upon glomerular breakdown with concomitant vascular readjustment, these vessels only existing in relatively small numbers in the normal mammalian kidney. The lack of agreement among the investigators is explained by Mc Callum as being due to the failure to consider only perfectly normal material. He pointed out that investigators working with young, carefully selected animals have found only a relatively small number of non-glomerular vascular connections, and that these have been shown to increase with age and disease.

From his careful microdissection studies of the aged and diseased kidney Oliver (1939) arrived at similar conclusions. Similarly, Loomis and Jett-Jackson (1942), working with Oliver's techniques, demonstrated the existence of abundant by-passing vessels, sometimes partially entering the partially fibrosed glomerulus near the edge of infarcts in the kidney. These

bypasses were thought to be a development of previously existing pathways, which tended to enlarge with use.

The detailed study of the vessels of the rabbit and of the human kidney with the neopren injection method by Trueta, Barclay, Daniel, Franklin and Prichard (1946) showed the efferent arteriole of the juxtamedullary glomerulus to be just as large or often even larger than the afferent one of the same glomerulus, this in sharp contrast to the condition of the vessels of the cortical glomerulus. In some cases the juxtamedullary glomerulus had two efferent vessels. The efferent vessels of the juxtamedullary glomerulus break up to form the arterial vasa recta of the medulla. The authors thus concluded that the juxtamedullary vascular system in man is of such a capacity that it may carry considerable amounts of blood diverted from the cortex to the medulla, in analogy with the functional mechanism, conclusively proven to exist in the rabbit. Many of the juxtamedullary glomeruli showed stages of degeneration, the final stage of which was that the afferent and efferent vessels formed one continuous trunk of a comparatively large calibre with a slight bend having some remnants of the glomerulus attached to its convex side. These abnormal forms were very common in elderly people and in some pathological conditions. In some, even the remnants of the glomerulus had disappeared, and the authors considered that the arteriae rectae verae represent the end-stage of this degenerative process. These changes were found much more often among the juxtamedullary than among the cortical glomeruli. The authors hold that these degenerating glomeruli and the arteriae rectae verae must affect the intrarenal distribution of the blood flow by presenting a large and easy pathway through which the blood may be diverted from the cortex. The implications of such a mechanism for quantitative excretory studies have been touched upon by the authors and will be further commented.

A further alternative channel by which the blood may by-pass the glomeruli is offered by the arterio-venous anastomoses, which according to the injection experiments by Spanner (1937) were much more numerous than formerly believed. Spanner thought that these anastomoses afforded possibilities of a retrograd perfusion of the tubular capillary bed when the glomerular circulation for some reason had been shut down. Trueta and his associates failed to find the arterio-venous anastomoses described by Spanner, and considered that, if they actually existed, these anastomoses could not be more than an occasional feature.

Attempts to review the very controversial literature on the juxtaglomerular apparatus of Goormaghtigh are omitted, as the questions of the existence and possible significance of this body seem to have no immediate importance for the problems discussed in this paper.

Physiology of Normal Renal Circulation.

Detailed problems of renal physiology have been given rather divergent explanations, presumably owing in the main to the approaches having been made under dissimilar experimental conditions and by different methods of measurement. With a modified type of Ludwig's stromuhr attached to the renal vein Burton-Opitz (1916) confirmed the earlier found presence of constrictor fibres in the greater splanchnic nerve, while no vasomotor fibres could be demonstrated in the vagus nerve. The renal innervation was further demonstrated to be unilateral. On contralateral stimulation of the splanchnic nerve there was an initial increase of the circulation in the non-stimulated kidney, which was attributed to the simultaneous rise in the general blood pressure. There was a subsequent decrease of the blood supply to the non-stimulated kidney, which was interpreted as a constriction of the renal blood vessels by the adrenalin released by the stimulation of the contralateral splanchnic nerve.

A considerable number of investigations reviewed by Smith (1939), in which use was made of the oncometric method, the stromuhr, renal arteriography and the thermostromuhr of Rein, have established the existence of a rise in renal blood flow after denervation in anesthetized animals. These findings clearly demonstrate the occurrence of a vasoconstrictor tonus in the operated and anesthetized animal, but, as Smith points out, they lack direct evidential value for the normal resting condition.

Milliken and Karr (1925), however, working with both anesthetized and unanesthetized dogs and collecting urine with ureteral catheters, demonstrated a rise in renal function even in those cases in which neither anesthesia nor cannulation had been used. This increased function was shown to persist for several months.

Using Rhoad's technique of explanting the dog's kidney and thus making the renal vein accessible, Van Slyke, Rhoads, Hiller and Alving (1934) calculated the renal plasma flow from the clearance of urea and its extraction ratio. In these painlessly conducted experiments no significant change was found in blood flow after denervation. However, in four cases there was a higher urea concentration in the renal venous blood than in the arterial, thus possibly indicating a reabsorption from the kidney. As a possible explanation of this phenomenon these workers thought that trauma during the needling of the renal vein may have caused a reflex paralysis of the tubular cells, these losing their relative impermeability to diffusion of urea from the tubular lumina back into the blood. To the present writer, however, it seems that a method which is thought to be able to give profound changes in the tubular permeability might just as well cause reflex changes in the renal blood flow.

Smith, Rovensteine, Goldring, Chasis and Ranges (1939) likewise failed to find any increase in the effective renal plasma flow as measured with the diodrast clearance method in man under high spinal anesthesia at a mean blood pressure decrease of 14 mm. However, Lamport (1941), adopting his formulae for renal resistance on the data of these workers, considered that a definite decrease of renal resistance could be demonstrated.

The objections to drawing conclusions from experiments on anesthetized animals, in which the method of measurement has involved considerable interference with the normal relations of the kidney, and the failure to demonstrate denervation hyperemia in the unanesthetized animal or man with the indirect methods, where instrumental interference with the renal circulation at the actual time the measurements were made was avoided, led Smith (1939) to conclude that there was no good evidence for tonic activity in the vasoconstrictor paths to the vascular bed of the kidney. This statement was made with the very important reservation that it applied to the horizontal, resting position.

Adrenalin was found by Richards and Plant (1922) simultaneously to cause an increase in the perfusion pressure and an expansion of the kidney volume when the rabbit's kidney is perfused at a constant rate. As a possible explanation of this seemingly paradoxical action of adrenalin Richards and Plant suggested that the drug acted predominantly on the efferent glomerular arterioles, thus causing engorgement of the glomerular tufts. In their direct observations on the frog's kidney Richards and Schmidt (1924) and Richards, Barnwell and Bradley (1926) could demonstrate that adrenalin in minute amounts caused the glomerular tufts to enlarge and to appear more densely congested with blood cells. From these studies the inability of the oncometric method to cope with the peculiar features of the renal circulation is evident.

The introduction of Rein's thermostromuhr (1927) was certainly an improvement over earlier methods, although it still involved the disadvantage of instrumental interference with the renal circulation. Indeed, most of the investigations by the Rein school in the subsequent years were made in the form of acute experiments on anesthetized animals. However, a number of important observations seem to have been made in these studies.

Hartman, Orskov and Rein (1936) demonstrated a practically unchanged renal blood flow in spite of very considerable systemic pressure changes brought about by vagus stimulation, high pressure perfusion or exclusion of the carotid sinus. After an instantaneous, very transient change, the renal circulation promptly returned to its original level. After complete denervation the renal circulation still exhibited a considerable autonomy to systemic pressure changes. A consistent and considerable reduction of renal

blood flow was found during the inhalation of carbon dioxide. This effect was completely abolished after total denervation of the kidney, and this circumstance was later used by these workers as a test of the success of the denervation. Thus, the action of carbon dioxide was considered to be centrally on the vasomotor centres, and the authors advanced the suggestion that the autonomy of the renal circulation was only put out of play in situations of catastrophe, as for instance asphyxia.

From thermostromuhr studies on the action of adrenalin, histamine and reflex systemic pressure changes Unna (1935) concluded that the direct renal vascular action of the drugs determined the changes in renal blood flow and that considerable systemic pressure changes had very slight influence. Stierlen (1936) found no reactive hyperemia after partial constriction of the kidney circulation. As a possible explanation of this he pointed to the enormous blood flow high above the oxygen demands of the organ and the illustrative high renal venous oxygen content.

Springorum and Centerea (1937) and Springorum (1938) extended the studies of the action of CO_2 on renal blood flow and diuresis. CO_2 was added to the inhaled air in an amount adjusted to give a clearcut rise in blood pressure. From the description of the authors it does not appear that asphyctic amounts were used, as has been suggested in the literature. The effect on the innervated kidney was found to be the same, whether the kidney was under basal conditions or under strong diuretic effect. Contrary to the case with most other vasoconstrictor agents, the reduction of blood flow was equally divided between both kidneys. In spite of the blood pressure rise there was a considerably decreased urine flow. Even in face of a considerable blood pressure rise the kidney under basic conditions showed a reduction of blood flow, which could amount to about 50 per cent at the end of the CO_2 inhalation. One hour after the injection of urea there was a considerably raised blood flow and diuresis, but a fresh inhalation of CO_2 produced anew a pronounced decrease of the blood flow and diuresis.

In his work of 1938 Springorum, using very small doses of adrenalin and CO_2 , could show that the decrease in urine flow did not depend upon the decrease in blood flow, as it could be produced without any changes in the latter. It was further confirmed that the CO_2 -effect was completely abolished after total denervation of the kidney.

Measuring the pressure in the renal vein and the renal blood flow simultaneously, Springorum (1939) was able to show that neither sympatol nor histamine injections showed other renal venous pressure changes than those pressure falls naturally accompanying decreases of renal blood flow of varying degree. During the anuria produced in one kidney by relatively slight pressure against the vesical collum there were no changes registered

in either blood flow or renal venous pressure. Springorum concluded that a rise in renal venous pressure tending to show a functional significance of any existing arterio-venous communications was never found to occur. This result gained by an entirely different method of measuring seems to have a definite interest for the interpretation of information arrived at with the clearance methods.

Quantitative Excretory Studies of the Normal and the Diseased Kidney.

For current concepts and methods of quantitative excretory studies reference should be made to Smith's monographs of 1937 and 1943, and, in the Scandinavian literature, to the recent extensive reviews by Laake (1945), Hilden (1946), Hogeman (1948) and Raaschou (1948).

For a full discussion on what substance comes closest to a true measure of the glomerular filtration reference may be made to the papers of Rehberg (1926), Smith (1937 and 1943), Ekehorn (1945 and 1946) and Hogeman (1948).

After the original contribution of Elsom, Bott and Shiels (1936) on the renal clearances of skiodan, diodrast and hippuran in the dog and of Landis, Elsom, Bott and Shiels (1936) in man, Smith and his associates established the suitability of diodrast clearance as a measure of the effective renal plasma flow in man. The assumption that the very high and identical clearances of diodrast and para-amino hippuric acid closely approached a complete clearance was proved by establishing the extraction ratio of para-amino hippuric acid in the human kidney, Bradley and Curry (1944) finding an average of 85 per cent, Warren, Brannon and Merrill (1944) an average of 88 per cent, Bradley and Bradley (1947) of 92.5 per cent. In the explanted dog's kidney, White (1940) found an average diodrast extraction ratio of 74 per cent, and Corcoran, Smith and Page (1941) one of 84 per cent, the latter authors considering it probable that White's lower figure was due to his data including observations at all plasma levels below 13 mgm per 100 cc. Van Slyke and associates (1948) found an average of 87 per cent for para-amino hippuric acid in the dog.

White, Findley and Edwards (1940) have treated the important question whether there occurs a rapid enough shift of diodrast from red cells to plasma during the renal passage to cause an appreciable error. At equilibrium after intravenous administration of diodrast they found the ratio:

D per 100 cc arterial cell water

D per 100 cc arterial plasma water

to average 0.32 in man. In man this ratio increased rapidly as the plasma level fell following cessation of the infusion of diodrast, giving figures as high as 1.20. The explanation of this rise of the ratio was taken to be that

the shift of diodrast from the cells to plasma is not rapid enough to keep pace with the fall of plasma D. The authors therefore estimated the cell contribution in man at less than half that in the dog with its higher red cell diodrast content, *i. e.* on the average less than 6 per cent. If extraction is complete in man, diodrast clearance should thus not exceed the renal plasma flow by more than 6 per cent. The incompleteness of plasma extraction would then tend to be balanced. Smith and associates (1945) showed that no definite penetration into the red cells was ever demonstrable in man in the case of para-amino hippuric acid, even in experiments lasting 3—4 hours. The identity of the diodrast and para-amino hippuric acid clearances would argue against any significant quantity of diodrast moving out of the red cells during renal passage. The incompleteness of the plasma extraction of diodrast during renal passage has been thought to be due wholly or partly to the fact that some of the blood in the renal vein has passed through non-excretory kidney tissue, pelvis, capsule and connective tissue (Smith and associates). It seems permissible to conclude that the evidence indicating that the diodrast clearance is a close measure of the effective renal plasma flow is well established in the case of the normal kidney.

To what extent diodrast clearance continues to give a close measure of the effective renal plasma flow in advanced cases of kidney disease seems a difficult problem. The deep-reaching nature of the rebuilding of the kidney architecture in terminal chronic Bright's disease as demonstrated by Oliver (1942) in his microdissection studies, and the entirely different functional behaviour of nephrons of abnormal structure towards trypan blue, induced Oliver to caution against injudicious interpretation of the results of functional tests in advanced renal disease. It can of course be argued that observations on terminal forms of hemorrhagic Bright's disease cannot be transferred to and considered valid in kidneys with less advanced organic disease, where the functional tests have their greatest theoretical and practical interest. Smith (1941) pointed out that functionally inactive tissue will not affect the significance of the ratio C_D/T_{MD} . Bradley (1944) pointed out that in renal disease blood perfuses a smaller and smaller mass of excretory tissue, relative to the nonexcretory, and that over-all extraction ratios would be expected to decrease. Extraction ratios as low as 55 per cent have been registered in a case of chronic glomerulonephritis, where the over-all renal function was not greatly impaired. Bradley, however, considers it unlikely that at the low plasma levels used the capacity of any perfused and still functioning tissue is overtaxed, and that the diodrast clearance thus measures the blood flowing to residual functioning tissue.

Studies on the behaviour of the tubular diodrast excretion at rising plasma diodrast concentrations have revealed essentially unchanged tubular perfusion in a limited number of hypertensive subjects, although studies of glomerular activity by means of measuring the tubular glucose reabsorption on rising plasma glucose curves in the same cases tended to show definitely abnormal conditions, suggesting a changed pattern of glomerular activity (Smith, Ranges, Chasis and Goldring, 1941, Smith 1943).

In chronic glomerulonephritis Earle, Taggart and Shannon (1944) found a falling-off of the observed values from the normal curve as the diodrast load approached diodrast Tm only in the cases with the most severe reduction of renal function, *i. e.* those with a TmD below 5 mg per 100 cc.

In a limited series of miscellaneous kidney disorders Josephson found the proportion between the tubular diodrast load and the TmD to be of the same order of magnitude as in normals (1947).

In chronic pyelonephritis Raaschou (1948) found normal tubular dispersion and normal levels for the self-depression and saturation limits, even in cases with very severe reduction of renal function.

Thus, there is evidence, although only such supported by a limited number of cases, that the remaining functional tubular tissue continues to handle diodrast in the same fashion as the normal tubules.¹⁾

The Influence of Various Factors on Renal Hemodynamics in Normals.

From the study of a number of agents Smith (1943) concluded that the renal circulation generally remained stable. Adrenalin, however, caused a marked decrease of effective renal plasma flow with a practically unchanged filtration rate. "Pyrogenic inulin", whether the fever response had been abolished by premedication with amidopyrine or not, produced a very pronounced increase in blood flow with an unchanged filtration rate. These findings pointed to the efferent arteriole being the prime regulator of the renal blood flow. Essentially the same response as that due to adrenalin was noted in two subjects, who by chance became very alarmed and apprehensive during the course of the clearance experiment. On the other hand, change from the horizontal to the upright position brought about a practically immediate reduction of both filtration rate and effective renal plasma flow, which, as it occurred simultaneously with a raised mean pressure, was interpreted as a vasoconstriction in which the afferent

¹⁾ Since this was written there seems to have been submitted crucial information pointing towards the existence of a maintained extraction ratio in essential hypertension (Reubi and Schroeder, 1948; Bradley, 1948).

arterioles participated. Brun, Knudsen and Raaschou (1945) found on an average 20 per cent reduction of the inulin clearance in the 60° one hour tilting test and 20—45 per cent reduction in diodrast clearance in the passive standing position. Although there were simultaneous increases in the hemoglobin content, the viscosity, cell volume and plasma protein content, amounting to about 5—10 per cent, these were considered unable to explain the changes in clearances.

In a few experiments on young adult males George A. Wolff (1943) could show that intense pain produced a prompt fall in C_D with a simultaneous although not quite so pronounced fall in C_M , the clearances remaining low for as long as forty minutes after the pain had ceased. The blood pressure during the pain period was elevated. The pain was produced by a head pressure device constructed so that multiple small, hard rubber pads could be applied to the head and screwed down tightly until an intense pain was produced.

Barclay, Cooke, Kenny and Nutt found reductions in the inulin and diodrast clearances, the latter ranging between 18 and 54 per cent, in eight normal subjects after running 440 yards at maximum speed.

Thus, judging from the above-cited studies, pain, exercise and change from the horizontal to the standing posture seem to give a reduction of both the inulin and the diodrast clearances, giving a pattern of renal hemodynamic alteration which differs somewhat from the one registered during the action of adrenalin as well as from that found in the two cases examined by Smith during apprehension and alarm.

Stability or Intermittency of the Filtering Bed of the Kidney.

The intermittency of the glomerular circulation demonstrated by Richards and Schmidt in the frog's kidney has reopened earlier arguments as to whether the extent of the filtration surface in the kidney is also variable in man and other mammals. Richards and Schmidt (1924) showed that the fraction of glomeruli open to the circulation in the frog's kidney could be increased by vasodilator agencies, *e. g.* caffeine, and decreased by various vasoconstrictor influences such as intense electrical stimulation of sympathetic fibres to the kidney and slow intravenous injection of adrenalin.

In 1922, Khanolkar, using injections of iron-ammonium citrate, carmine and hemoglobin solution and killing the rabbits after a few minutes, showed an uneven distribution of the substances, all glomeruli not being stained. More glomeruli were stained during the action of a diuretic (salt solution + caffeine sodium benzoate). Hayman and Starr (1925), using

Janus Green B, confirmed the results of Khanolkar. After inhalation of 10 per cent carbon dioxide the glomeruli stained numbered 50 per cent of the total. In another experiment a higher concentration (unknown) reduced the number of glomeruli stained to 9 per cent of the total. White (1939), however, in dogs and rabbits found that either all glomeruli were injected or else the distribution was such as to favour the interpretation that failure of injection was caused by a random distribution of the india ink in the larger preglomerular vessels.

Recently Trueta and his associates (1947) demonstrated that the blood has two potential routes in the rabbit's kidney, one cortical, one medullary. By a number of different methods of study during tourniquet occlusion of the hind limb, stimulation of a sciatic nerve or the nervous plexus surrounding the renal artery or injection of various vasoconstrictor drugs, and by demonstrating the intimate structure of the vascular pathway affording the means for a medullary redistribution, a very conclusive picture was formed.

Thus, in amphibia and among mammals in the rabbit the evidence for glomerular intermittence and variability of the filtering bed, even to the point of a fundamental intrarenal re-distribution of the blood, seems well-founded, although not unanimously accepted. Trueta and his associates, using a number of observations from human pathology and demonstrating in the human kidney juxtamedullary vascular pathways, which are thought to be anatomically large enough to provide means for a medullary redistribution of blood, have now opened the question whether a similar mechanism exists in man and could be regarded as operative in essential hypertension and shock.

In the dog Van Slyke (1948) found that in acute hemorrhagic or traumatic shock the kidneys continued to extract para-amino hippuric acid to the normal degree until the shock was so severe that the renal blood flow was decreased below 5 per cent of normal. In shock experiments on dogs produced by tourniquet Corcoran, Taylor and Page (1943), however, in some instances noted a depression of the extraction ratio of diodrast when the tourniquet was released. After total clamping of the renal artery a consistent depression of the extraction ratio has been established (Selkurt, 1946; Van Slyke, 1948).

In man the question of the stability of the filtration bed has been subjected to analysis by Smith and associates (1943) with their saturation methods. Smith pointed out that, when filtration is completely arrested in a glomerulus, the attached tubule will no longer participate in the reabsorption of glucose, and the T_{mg} will decrease in proportion to the glomeruli closed independent of the rate of filtration in the remaining nephrons. Caf-

feine, adrenalin and "pyrogenic inulin" caused only very small and inconclusive changes in the T_{mc} . The marked changes in plasma flow produced by adrenalin and pyrogenic inulin should reasonably give evidence of an alteration in the pattern of glomerular activity if a significant number of glomeruli were involved in a system of intermittent activity. Caffeine, which has been shown to open up glomeruli in the frog's kidney and which was shown by Smith to produce on an average a 15 per cent increase in the total glomerular filtration rate in man, caused no change in the T_{mc} . The same procedures caused no change in the T_{mD} either, although Smith considered this fact to have less evidential value, as the rôle of the interstitial fluid in the perfusion of the tubules is not entirely clear, the possibility remaining that the tubules from inactive glomeruli could still participate in the T_{mD} .

Abdominal pressure (Bradley, 1947) produced decreases of inulin and diodrast clearances and T_{mD} with no change in the simultaneously recorded extraction ratio.

As the decreases of the extraction ratios found after total clamping of the renal artery might just as well be explained by tubular changes of permeability allowing rediffusion of diodrast, the hitherto available evidence from dog and man seems rather to argue for a comparatively stable filtering bed and against intermittent glomerular activity or patterns of fundamental redistribution of blood in the interior of the kidney.

Renal Hemodynamics in Essential Hypertension.

Reference is made to the recent review of Hogeman (1948) for experiments using the phenolsulphonphthalein test, the creatinine clearance, urea clearance and maximal concentration capacity.

A number of papers by Smith and associates have been summarized by Smith (1943) and in the monograph of Goldring and Chasis (1944). They expressed the view that changes in renal hemodynamics were found early in hypertensive disease. The earliest change was considered to be a diminution in the T_{mD} . Associated with this there was in most cases a reduction of C_D , while C_m was within the normal range in the early stage of the disease, leading to an increased filtration fraction. In the majority of the hypertensives the ratio C_D/T_{mD} is below the mean normal value, which in the presence of an elevated mean pressure must have its explanation in an increased resistance in the kidney, the rise of the filtration fraction pointing to an increase of resistance in the efferent arteriole. The marked increase in diodrast clearance and the fall of the filtration fraction induced by pyrogenic inulin in all but a few very advanced cases suggested a

functional vasoconstriction rather than fixed structural lesions. The failure to register any changes after sympathectomy was considered to argue for humoral and against neurogenic factors as the cause of the increase in resistance.

Chesley and Chesley (1940) found in the majority of 37 hypertensive women a considerable reduction of C_D , but some cases presented no decrease or only a slight one in C_D and a normal filtration fraction. Steinitz (1941) stressed the influence of cases with severe renal lesion on the average values in his small material (9 cases) and concluded that renal ischemia is not necessarily present in essential hypertension. Foa, Woods, Peet and Foa (1942) confirmed the finding of reduced C_D and increased FF in 20 hypertensives, and found the reduction in C_D to show a definite correlation to retinal changes, degree of thickening of systemic arterioles, and systolic and diastolic blood pressures. On the basis of 30 observations in 17 patients after supradiaphragmatic sympathectomy they concluded that the level of effective renal blood flow persisted despite a reduction of blood pressure, which opened the possibility of dilatation of the renal arterioles. There was a decrease of FF in 8 of 15 patients. They also touched upon the probability that no changes in the state of the arterioles could reasonably be expected when the reduction was due predominantly to sclerosis or hypertrophy of the vessel wall.

In six patients, after extensive paravertebral sympathectomy, Adams, Alving, Sandeford, Grimson and Scott (1941) found evidence of renal arteriolar dilatation only in one, while in one no reduction in C_D was apparent before operation. Findley, Edwards, Clinton and White (1942) in 12 subjects under the age of fifty years with uncomplicated essential hypertension found absence of renal ischemia in a high proportion of cases. They further expressed the belief that high filtration fractions in hypertension depend more on diminished diodrast extraction than on increased filtration pressure. In a study of 5 patients after various types of sympathectomy they stated that no appreciable change of renal pattern had been found.

Friedman, Selzer and Rosenblum (1941) examined patients with long-standing (>10 years), «early» (<6 years) and variable hypertension in which, although no definite elevation of blood pressure was present at the time of the renal study, the authors had found varying elevated values during a year preceding the renal study. In the great majority of the cases there was a moderate reduction of C_D , although the C_{In} was not materially diminished. No significant difference was found between the long-standing and the early group, while the clearances were within the normal range in two of the cases of variable hypertension, in which the diastolic pressure had dropped to below 80 mm at the actual time of the renal study.

In the mixed series of normals, hypertensives and cases of aortic coarctation, groups with the higher diastolic pressures showed the higher filtration fractions.

Talbott, Castleman, Smithwick and Pecora (1943) showed a good correlation between clearance results and biopsies made on kidney specimens taken during sympathectomy in a study of 20 patients, the clearances being practically normal in the cases with renal vascular disease graded 0—1. Filtration fractions were normal in 7 out of 8 cases in biopsy groups 1, 2 and 3. Bilateral lumbodorsal sympathectomy had relatively little effect on clearances measured in the resting horizontal position. Although glomerular filtration was reduced about 20 per cent in the immediate postoperative period, it then returned to and continued to maintain its preoperative level. Renal plasma flow was essentially unchanged.

In 37 patients with benignant hypertension Hilden (1946) found C_D to be normal in the great majority, while with one exception his 23 cases of malignant hypertension showed a decreased C_D and an increased urea/diodrast clearance ratio. There was a definite correlation between severity of symptoms and reduction of C_D .

Hogeman (1948) in a series of 62 cases found the same type of functional change. In his series approximately 25 per cent did not show a raised filtration fraction. There was no significant difference between cases with a known duration of more than three years and those with shorter duration.

Corcoran, Taylor and Page (1948) classified their material of 183 cases of hypertension into arteriosclerotic, malignant and essential hypertension, subdividing the last-mentioned group by the amount of extrarenal vascular lesions demonstrated as early or established. They concluded that the change of renal pattern in early essential hypertension was purely functional, with neither renal ischemia nor loss of nephrons and with vasoconstriction extending only to the afferent arteriole. The calculated increase in renal resistance amounted to 33 per cent, which would account for about 30 per cent of the increase in total peripheral resistance in these cases. In the phase of established essential hypertension they considered arteriolar sclerosis to be present with consequent renal structural loss and concurrent vasoconstriction of afferent and efferent arterioles. There was usually evidence of some ischemia of the tubular areas remaining in function. Glomerular filtration pressure was increased. The changes present in the established essential phase were greatly exaggerated in malignant hypertension, in which group, however, the scattering of the renal functional data was considerably more skewed. In an earlier study of two cases after lumbodorsal sympathectomy Corcoran and Page found no increase in renal blood flow postoperatively.

Summarizing, the papers reviewed above report about 500 cases of essential hypertension investigated with the inulin and diodrast methods, with the exception that Hilden used urea instead of inulin. It may be safely stated that the vast majority of cases showed a definite decrease in C_D with a less pronounced decrease in C_{In} , leading to an increase in filtration fraction. The low ratios of C_D/Tm_D found by Smith and associates (1940) and by Corcoran, Taylor and Page (1948) for their groups of established and malignant hypertensives would seem to afford evidence for the presence of a relative ischemia in the residual functional tubular tissue.

On the other hand, in all the materials reviewed there are considerable numbers of cases of well established hypertension presenting a C_D at or moderately below or even slightly above the normal mean. Among those materials in which a classification based upon variability of blood pressure or other extrarenal symptoms was made values within the normal range were found predominantly among: (1) Findley, Edward and Clinton's subjects of uncomplicated hypertension below 50 years, (2) in some cases of Friedman and co-workers, which on bed rest dropped to a normal blood pressure, (3) among Hilden's cases of benignant hypertension and (4) in Corcoran, Taylor and Page's group of "early hypertension" with insignificant or no evidence of extrarenal vascular disease.

The importance of the finding of a not inconsiderable number of cases with normal values for C_D is further accentuated by the demonstration of the downhill trend occurring in the structure of the kidney of normals mainly past the age of 40 (anatomical studies by Oliver, 1942; Bell, 1947; functional, by Cox and Dock, 1941; Goldring and associates, 1941; Shock, 1946 and Hilden, 1946). The larger materials published of normals, being mostly composed of young people and chiefly of males, will tend to make the differences larger than a comparison material of cases belonging to the same age-groups as the series of hypertensives.

In the literature available the author has been able to find 55 cases with studies of C_{In} and C_D before and after sympathectomy. Findley *et al.*, Adams *et al.*, Goldring and Chasis state that they found no change with the exception of one case in the series of Adams *et al.* Corcoran and Page found a slight decrease in their two cases, while Talbott *et al.* registered a decrease averaging 17 per cent within one year. Foa and co-workers found no significant change in their series, and in view of the average fall of blood pressure attributed this to a relaxation of renal resistance. Goldring and Chasis, Adams *et al.* and Talbott *et al.* gave no blood pressures taken at the actual time of the renal study. In four of the five cases reported by Goldring and Chasis (1944) studies on the separate kidneys after the first stage of sympathectomy showed slightly lower

values for C_D on the operated side. However, as the preoperative figures varied from 504 to 820 in the five cases, with an average of 613 cc/min., there seems hardly to have been evidence of any preoperative renal arteriolar constriction of a degree to afford evidence of any postoperative arteriolar relaxation.

The cases of Findley, Edwards and Clinton showed a very marked reduction in clearances, C_{in} averaging 61 and C_D 256 cc/min. The responses of C_D were + 2.5, + 33, + 26, + 16 and — 6 per cent, giving an average increase of 14 per cent. This was not considered significant by the authors. The average blood pressure figures were unchanged, 210/130 as compared with 208/131 postoperatively.

In Corcoran and Page's two cases there was a decrease of both clearances, the preoperative values for C_D being 310 and 415 cc/min. In the recumbent position there was a tendency to somewhat higher postoperative blood pressure readings in one and somewhat lower in the other case. In the material of Foa *et al.* there was a postoperative increase in the group with markedly reduced renal function, while the cases with moderately reduced showed a slight decrease.

Thus, no consistent changes in clearance values have been found after sympathectomy. For reasons which will be discussed later some of the series are difficult to evaluate owing to the lack of blood pressure data at the actual time of the renal study. In one series the preoperative values were so high that definite increases could hardly be expected. In one series the preoperative values are so low that in the light of other investigations (Talbot *et al.*, 1943) there is every reason to expect advanced renal vascular disease to have been present.

The problem of the possible rôle of the renal nerves in essential hypertension seems to offer considerable difficulties, which will be discussed to some extent later. The investigations reviewed give no direct support for the existence of a tonic vasoconstrictor activity of the renal nerves in the resting recumbent position in essential hypertension but, on the other hand, they can by no means be taken to exclude this possibility or still less the possibility of intermittent neurogenic influences playing a rôle.

Anatomy of the Renal Vascular Bed in Essential Hypertension.

For a full discussion reference is made to the works of Moritz and Oldt (1937), Bell and Clawson (1939), Fishberg (1944), Goldblatt (1946) and Bell (1947). Agreement seems to be general as to the frequency of definite arteriolosclerotic changes in the small arteries and afferent arterioles being very high in post mortem material, ranging in the larger materials

from 100 per cent in the 72 cases of Fishberg to 82.5 in those of Bell (1947). Reports on smaller series or isolated cases of essential hypertension, even of a long-standing variety, without arteriosclerotic changes, have been reviewed by Fishberg (1944). In only about 50 per cent of biopsy specimens taken during sympathectomy did Castleman and Smithwick (1943) find vascular changes that they thought sufficient to produce renal ischemia. The validity of the biopsy method was seriously questioned by Goldblatt (1946), who maintained that as yet the evidence against renal vascular changes being the primary cause of essential hypertension was not sufficient.

For a discussion of the problems of stenosis or apparent stenosis of the main renal arteries or larger intrarenal arterial vessels, reference may be made to the papers of Blackman (1939), Oppenheimer, Klemperer and Moschkowitz (1939) and Richardsson (1943).

On the strength of their kerosene-perfusion studies Cox and Dock (1941) claimed that most kidneys from patients with non-uremic hypertension had vascular beds in the normal range, although a few showed great decreases in the capacity of flow. They interpreted this as indicating that renal arteriosclerosis is often a result and rarely a cause of hypertension. They further believed significant occlusion of large renal arteries to be rare.

For a discussion of the intimate structure of the afferent and efferent arterioles and the glomeruli, reference may be made to the papers cited above by Bell and Clawson, Moritz and Oldt, Trueta *et al.* as well as Mc Gregor (1936). As regards the discussion of the functional studies to be presented it will only be remarked that Bell and Clawson conclude that extensive deposits of hyaline must undoubtedly narrow the lumen of the arterioles and interfere greatly with the power of the circular muscle to regulate their calibre. On the other hand, Mc Gregor showed the efferent arterioles to be normal in serial sections. *From the morphological appearance of the two sets of arterioles it seems quite possible that on account of the physical state of their walls they might react differently to the same constricting or dilating agent.*

From the reviewed anatomical and functional studies it seems to the author as if the bulk of evidence definitely argues against renal arteriosclerosis being the sole or even a major contributory prime mover in the development of essential hypertension. It seems equally clear that no evidence of renal ischemia is found in many uncomplicated or "early" cases when examined in the resting state. It also appears as though there is a lack of data on renal hemodynamics in essential hypertension in conditions of stress, physical activity, alarm, pain, cold, standing position as well as a variety of other conditions in which experimental approach can be conceived as feasible.

CHAPTER II.

Plan of Investigation.

The consistent and considerable renal vasoconstrictor effects that Rein and his school found carbon dioxide to have on the dog suggested that it would be profitable to examine the action of this agent on renal hemodynamics in man by means of the clearance methods. The annihilation of the CO_2 action by renal denervation seemed to correspond with what is generally known of the vascular action of CO_2 . This fact combined with the considerable B.P.-raising effect CO_2 is known to have made a study of this kind appear rather representative of at least some types of centrally acting, neurogenic B.P.-raising factors on renal hemodynamics. The original plan of concentrating the study to early cases of essential hypertension had to be abandoned, as, owing to the great shortage of beds, it was impossible to hospitalize cases of this type in sufficient numbers for the purpose. Some early results seemed, in fact, to justify direction of attention to more advanced cases of primarily benignant hypertension.

On The Action of Carbon Dioxide on the Vascular System.

For the studies of the site and mode of the B.P.-raising action of CO_2 reference may be made to Dale and Evans (1922), Heymans, Nowak and Samaan (1934), Nowaks and Samaan (1935), for a discussion of the therapeutical application, to Goodman and Gilman (1940). Briefly put, Dale and Evans found that forced rapid ventilation in the anesthetized cat produced a considerable fall in blood pressure, which was rapidly restored when the air was replaced by expired air. The fall of the blood pressure was accompanied by the swelling of a loop of intestine, enclosed in a plethysmograph, shrinkage immediately occurring when expired air was substituted, thus illustrating the vascular changes that had occurred in the splanchnic area. While the cat after section of the cervical cord showed essentially the same response, the animal with its medulla destroyed was affected in the opposite direction; excessive ventilation with pure air caused a small rise of pressure while a change to expired air was followed by a fall.

The vasoconstrictor action of CO_2 in the splanchnic area seems well established in the experimental animal, for the intestinal loop by Dale and Evans, for the kidney by the Rein school, as mentioned earlier.

In contrast to this stands the powerful vasodilator influence of CO_2 , shown for the pial vessels by Wolff and Lennox (1930), for various regions

in the brain of the cat and the rabbit by Schmidt and Hendrix (1937), and for man by Lennox and Gibbs (1932). The last-mentioned authors recorded the changes in the arterio-venous oxygen and carbon dioxide concentrations (femoral artery, internal jugular vein). This cerebral vasodilator action in man has been recently confirmed by Kety and Schmidt (1945) with their indirect nitrous oxide inhalation method, this method having been subjected to a comparison with the direct method of the bubble flow meter in the monkey.

Thus, it seems fairly well established, at least in some species of experimental animals, that CO_2 has a directly opposite effect on the cerebral as on the splanchnic circulation.

An extensive study of the effect of CO_2 in hypertensives has been made by Raab (1929). While hyperventilation produced no significant decrease of blood pressure in normals, it always gave a decided decrease in the pressure of hypertensives. The fall in blood pressure did not occur when the hyperventilation was effected with a CO_2 -containing mixture. The blood-pressure rise during the inhalation of CO_2 was approximately thrice as pronounced in hypertensives as in normals, while the frequency and depth of respirations did not show any significant difference between the two groups. No or only a slight decrease in blood pressure was found to occur on hyperventilation in nephritis with hypertension. Raab interpreted his findings as due to an increased sensitivity of the vasomotor centres to the action of the normal, arterial CO_2 content as well as to the increased content during inhalation of the gas.

Hardgrove, Roth and Brown (1938) confirmed that the blood pressure rose considerably more in hypertensives than in normals. They did not speculate on the mechanism. None of these investigators apparently encountered any untoward reactions of importance due to CO_2 .

CHAPTER III.

Methods.*Sampling*

While the chemical determinations were performed in exactly the same fashion throughout the investigation, the clearance procedure was changed a couple of times, as the technique first used did not appear satisfactory for the purpose.

About 30 tests were first performed with a single intravenous injection of diodrast ("Umbradil", Astra), the technique used being essentially the same as that extensively discussed by Hogeman in a recent publication (1948). The periods varied between 20 and 30 minutes. During one period carbon-dioxide was administered, either after two basal periods or between them. In the latter case 8—10 minutes were allowed to pass before the next clearance period was started. The successive drop of the clearance values described by authors using the single intravenous injection (Hogeman; Raaschou, 1948) was encountered and, as this naturally rendered the evaluation of any changes evoked by the CO_2 inhalation very difficult, the technique was abandoned. Still, as some observations of interest were made, the results will be briefly discussed later.

After this mode of procedure was abandoned all subsequent studies were made with a technique rather closely following the one used by Smith and associates, as described in a number of papers, for instance the monograph of Goldring and Chasis (1944). Some of the first experiments were run with diodrast only, all subsequent ones with inulin and diodrast simultaneously.

In about two-thirds of the experiments two or sometimes three basal clearance periods of about 20—30 minutes' length were run, the period of CO_2 inhalation mostly being placed between the basal observations, in which case 8—10 minutes were allowed to pass before the next period was started. In about 30 of the last experiments, as a rule five basal and two CO_2 inhalation periods were run, in which case the basal period sandwiched between the CO_2 periods was started immediately after the first CO_2 period was finished. Minor points of technique were varied during the course of the investigation, as for instance the amount of saline solution used for the bladder washout, or the type of catheter, tubing and clamps used. As the technique finally arrived at proved on the whole most satisfactory, and as the practical points of clearance work with continuous intravenous infusion have not been very extensively discussed in the Scandinavian literature, full particulars of the technique used will be given below.

All clearance experiments were performed in a special room, care being taken to cut down extraneous sources of disturbance as much as possible. A Kelly infusion bottle having a volume of 700 cc was suspended, freely rotating, from a one meter long bar attached freely movable to the wall of the examination room. Thus, the patient can be brought to the examination in his own bed, and the work around the bed is not hampered by standing tripods. For the regulation of the drip a 4-inch tunnel clamp was used.

Blood samples were drawn from an indwelling needle in the cubital vein of the other arm.

The urine was collected from an indwelling catheter, this being of a six-hole variety. After suprapubic pressure, 20 cc of saline were given as a bladder washout, this being drawn back into the syringe, whereby the volume of the fluid gained gave a fairly good

idea of the completeness of the bladder-emptying. After this, some 50 cc of air were injected and then expelled by renewed suprapubic pressure. Sometimes, when there was an impression of incomplete emptying, a slight sliding forth and back of the catheter could result in a second outpouring of washout fluid.

It was found most practical to insert a tight coupling of the Yale B. D. LOK-device between the catheter and "the washout syringe", this preventing any losses of urine.

After each bladder-emptying the experimenter's hands were washed before drawing the next blood sample. With rather few exceptions the author carried out the bladder-emptyings himself. In spite of all these precautions mentioned it is his personal impression that difficulties in bladder-emptying constitute the largest and most important sources of error in the clearance methods.

Before the intravenous infusion was started a plasma blank was drawn. The following blood samplings were spaced with as equal intervals as possible during the clearance procedure, one of them always being taken close to the end of a CO_2 inhalation period in order to catch any changes in plasma concentration that might occur during the action of CO_2 . Care was taken to use as little stasis as possible. As an anticoagulant 0.1 cc of heparin solution (5 per cent) was used. The blood samples were centrifuged as soon as possible.

As a priming dose usually 2 cc of a 35 per cent diodrast solution and 20 cc of a 10 per cent inulin solution were used. Immediately afterwards the sustaining solution, consisting of 5—8 cc of 35 per cent diodrast and 50—80 cc of 10 per cent inulin dissolved to a volume of 700 cc of physiological saline solution, was instituted, the drip rate adjusted to give a flow between 2.5—4.5 cc per minute according to the clearance levels expected. It is the author's impression that this method ensured just as level blood-concentration curves as elaborate calculations on the basis of body-weight and calculated available fluid. The most important point in this connection seemed to be that a careful clinical analysis before the clearance test enabled a close guess to be made of the clearance values to be expected. With this method plasma diodrast values ranged from 1 to 3 mg per 100 cc and plasma inulin values from 20 to 50 mg per 100 cc. After the priming injection had been run in, 25—30 minutes were allowed to elapse before the first clearance period was started, 4—5 washouts with 20 cc of physiological saline being used to get rid of the traces remaining of the highly concentrated urine produced during the high plasma levels immediately following the priming injection. When 7 or more clearance periods were used, the length of the periods averaged 10—15 minutes, longer periods only being used at low rates of urine flow in an attempt to reduce the error in bladder-emptying.

After three to five basal periods, a CO_2 inhalation period was introduced, the inhalation being started 2.5—3 minutes before the emptying was completed and finished about 2 minutes before the end of the period. After this a new basal and then one more CO_2 period were run without pauses.

The level of the blood pressure was determined sphygmomanometrically before the first CO_2 period by a couple of readings and then registered repeatedly at about 2—3 minute intervals during the inhalation. During the course of the investigation the aneroid manometer used was repeatedly checked against a mercury manometer, the latter also being used in cases where the systolic pressure was expected to rise to 300 mm Hg or more during the action of CO_2 .

During the series of experiments made with the single intravenous injection technique the type of mask and the composition of the oxygen-carbon dioxide mixture were varied, the range of the carbon dioxide concentration being from 4 to 10 per cent. As a rule, 10 per cent CO_2 -mixtures were not well tolerated towards the end of the comparatively long

periods (20—30 minutes) then employed, and it soon appeared that the mixture supplied for routine clinical use, "Carbogen" (6.5 per cent carbon dioxide in oxygen), was fully as satisfactory as any of the other mixtures tested. Hence this concentration was used in all the studies with continuous intravenous infusion.

Various masks were tried, from a type with a free outlet to a completely closed system. Since the individual tolerance was extremely variable, as was reasonable to expect in the mixed material of patients subjected to this investigation, it was occasionally necessary for the mask to be removed for a few seconds to allow the patient to breathe pure air. As this might also occur in nervous patients with a free outblow system and the weakest CO_2 concentrations, the idea of getting an absolutely standard CO_2 inhalation was very soon abandoned.

The procedure then adopted was as follows. A closed mask was used, covering nose and mouth with a rubber bag of 3.5 litres volume attached immediately to the mouthpiece. On the mouthpiece there was a fine-calibred outlet. A considerable rebreathing of the mixture was thus obtained, the final concentration of CO_2 reached being unknown. The aim was as strong a CO_2 effect, evidenced by deep and rapid breathing and a considerable rise of blood-pressure, as could be arrived at without too much discomfort. However, in some anxious subjects it proved necessary to remove the mask a couple of times for a few seconds. Three experiments had to be discarded on account of anxiety and lack of cooperation on the part of the patient, which made several long pauses necessary, thus causing the CO_2 inhalation to become insufficient to produce deep breathing and blood-pressure rises.

In three cases of essential hypertension with rather advanced cardiovascular disease there was distress of a degree to affect the result. CO_2 inhalation had to be stopped after a few minutes in a 55-years-old female owing to a bout of marked tachycardia. In two cases there was a distinct feeling of distress, sweating and distension of the cervical veins. In one of these cases the systolic pressure remained unchanged, in the other it fell slightly, while the diastolic showed approximately the usual rise. The urine flow fell sharply, in one case to less than one half, in the other to less than one third, of the control values. There was a simultaneous depression of inulin and diodrast clearances by approximately 30 per cent in both cases. As the aim was to investigate the effect of the blood pressure rise during administration of CO_2 on the renal function, and not on the cardiac, it was felt justified to exclude these two patients from the series. Moreover, at least in one of these cases the sharp reduction in urine flow made the observation during CO_2 inhalation very unreliable.

Only in the case of an extremely malignant hypertension in a 25 years old male was there a complication of any severity that could reasonably be ascribed to the experimental procedure, signs of a moderate intestinal bleeding starting a few hours after the completion of the clearance procedure. No really threatening condition developed. In the great majority of the experiments there was some headache after the CO_2 inhalation, which often persisted for one or two hours. *It may be of interest that some of the patients having severe hypertension with advanced vascular disease stated that their usual type of severe headache disappeared during and for some time after the administration of CO_2 .* This was especially striking in the case of a 60 years old male (G.B. J. 285/46) with severe hypertension, grade 3 fundi, and extensive signs of arteriosclerosis, who usually had a very severe and quite unresponsive headache. This patient requested to have a "Carbogen" tube at his bedside during the rest of his hospital stay. *On the basis of the rather unsystematized and few observations made it would be unwise to state that CO_2 can relieve headache in those cases of hypertension in which advanced*

cerebral vascular disease can reasonably be supposed to exist, but it may be profitable to penetrate further into this question. The great increase in normal cerebral blood flow described by Lennox and Gibbs as well as by Kety and Schmidt should tend to make a favourable response intelligible in these cases.

The rectal temperature was registered after the experiments. In four consecutive cases there was a chill and a rise of temperature to 38.5–40° C. Pyrogenicity of the particular batch of inulin used could be excluded, and the reactions disappeared after the tubing had been changed. In two of these cases, one normal control and one only slightly hypertensive, the filtration fractions ranged from 0.35 to 0.43, which was higher than in severe, malignant cases in this series. As it was not considered that the initial vasoconstriction shown by Bradley, Chasis, Goldring and Smith (1945) to occur in the renal pyrogenic response had been safely excluded, these four cases were discarded.

There appeared to be a possibility that CO₂ could change the cell volume/plasma ratio and thus affect the signification of the plasma clearance. Theoretically this could happen by vascular effects on the splanchnic circulation throwing deposited blood of another composition into the general circulation or by CO₂ increasing the permeability of the red cells (as shown by Hamburger, 1892) and thereby increasing their diameter (Price-Jones, 1920) and possibly their volume.

Unfortunately, no reliable equipment for hematocrit was available in this laboratory until towards the end of the investigation, and therefore studies using this method were only performed in a limited number of the last experiments.

In order to evaluate the possible changes due to the infusion fluid the hematocrit values are given in Table 1 for blood taken prior to infusion, B₀, for the last blood sample without CO₂ effect, taken after the infusion had

Table 1. Hematocrit during Inhalation of Carbon Dioxide.

B ₀	B ₂	B ₃ (CO ₂)	Average (B ₀ , B ₁ , B ₂)
31.0	27.0	27.0	28.0
45.5	46.0	41.0	43.0
42.0	39.5	40.5	41.0
50.5	48.0	48.5	49.0
40.5	39.5	41.0	41.0
43.0	45.5	43.0	45.0
38.5	36.5	38.5	37.0
39.0	39.0	37.0	39.0
38.5	41.0	40.0	39.0
44.0	41.5	43.0	44.0
44.5	39.5	40.0	44.0
54.5	51.5	53.0	54.0
46.5	41.0	43.0	46.0
51.0	49.5	51.0	51.0
43.5	42.0	42.0	43.5

been going on quite a while, B_{12} , and for the blood sample taken close to the end of a CO_2 inhalation period, B_{13} . Lastly, the three values for the control blood samples are averaged. The method was the one used by F. Nilsson (1948).

The results are considered to be indicative of a negligible influence of CO_2 on the hematocrit.

At the beginning of the investigation the hemoglobin percentage and the red cell count were determined in 12 cases before and at the end of the CO_2 inhalation. The average values are given below.

Table 2. Hemoglobin Percentage and Red Cell Count during Inhalation of Carbon Dioxide.

	Before CO_2	During CO_2
Hemoglobin Percentage	90	91
Red cell count	4.8	4.7

Thus, no significant differences in hematocrit, red cell count or hemoglobin percentage were registered after, on an average, 15 minutes' inhalation of CO_2 . From this point of view the plasma clearance should still hold the same relation to the whole blood flow during CO_2 inhalation as under ordinary conditions.

There remains a possibility that changes in the red cell permeability brought about by the CO_2 inhalation may affect the nature of the shift between red cells and plasma that probably occurs during the renal passage, thus deranging the significance of the figure for the plasma clearance. Direct proof on this point could only be gained by access to renal venous blood, which under the local conditions was technically impossible. Cubital vein samples collected during inhalation of CO_2 and centrifuged at rather varying times after being drawn did not show any characteristic differences from the control samples, which is believed to have some value on this point, though a very limited one. It may be mentioned that the samples were not drawn under oil, as the importance of this procedure had not been realized at that time. Some further indirect evidence that altered cell permeability due to CO_2 does not play such a rôle in causing a systematic error that the main conclusions need be invalidated will be further discussed later.

It could easily be argued that this elaborate experimental procedure could bring into play a psychogenic renal vasoconstriction such as that discussed by Smith (1943). This may be so, although only few patients showed any general signs of apprehension or fright during the procedure. As will be discussed, the average figure for the blood pressure during the clearance test was only slightly above the lowest recorded during the entire hospital stay. The discomfort caused by the mask and the distress due to CO_2 could easily be thought to have such an effect on the renal circulation. In order to throw some light on this question a few control experiments were performed, the same set of equipment being used but with inhalation of pure oxygen.

In three subjects with normal renal function and in one case of mild acute nephritis in the convalescence with a somewhat low filtration rate, the following results were registered.

Table 3. Renal Function during Inhalation of Oxygen.

	C_D			C_{In}			BP	
	Basal	CO_2	Per cent change	Basal	CO_2	Per cent change	Basal	CO_2
Normals								
A. G., m.	574	592	+3	89	91	+2	145/100	145/100
G. G., m.	489	523	+7	119	116	-3	—	—
G. B., f.	765	630	-17.5	145	112	-23	—	—
Ac. nephritis								
V. H., m.	542	554	+2	84	86	+3	110/70	130/80

It is seen that there was no significant alteration in three of the cases, while in the only female, G.B., there was a reduction of both clearances, which is believed to be significant. This patient, however, showed in the same experiment during CO_2 inhalation a decrease of C_D by 32 per cent.

It appears safest, however, to infer that the changes in renal hemodynamics registered during the inhalation of CO_2 need not in every case be exclusively due to the action of this agent on the nervous centres, since the discomfort and distress felt during the CO_2 inhalation may play some part. Certainly, this does not invalidate the CO_2 inhalation as a procedure for studying the renal hemodynamic response during neurogenic vasoconstriction.

Analytical methods.

Diodrast: For determining diodrast-iodine Alpert's method (1941) was used with some slight modifications. For principles, calculations and general discussion reference may be made to the paper of Alpert's.

In the early work some difficulties were experienced at the stage of oxidation. In spite of constant shaking and a rather long boiling start by hand, occasional sputtering of the bromine and consequent losses could not be avoided, even with the use of various types of antibumpers. Then bromized water was introduced instead of the pure element, which promptly eliminated all difficulties of this kind.

Reagents

Acid Zinc Sulphate Solution: 12.5 gm of $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ dissolved in 31.5 cc 1.0 normal H_2SO_4 and made up to one litre with distilled water.

Sodium Hydroxide, 0.75 Normal: In order to remove traces of iodine the saturated solution was shaken 8—10 times with absolute alcohol.

Bromized water: 0.40 cc of Bromine (Schering-Kahlbaum) was added to 10 cc of distilled water. Stocked conveniently in a glass-stoppered bottle kept under a hood. Shaken before use.

Phosphoric Acid (H_3PO_4): Kept in an ordinary dropper bottle.

Sodium Thiosulphate, 0.002 Normal: To 500 cc of this solution 5 cc of amyl alcohol were added. Kept protected from light and air. The stock 0.1 N solution was made up afresh approximately every second month. The 0.002 N solution was made up anew approximately every third week, when the titre usually began to show a slight decline.

Potassium Iodate, 0.1 Normal. Stock Solution: 3.567 gm of KIO_3 were dissolved in one litre of distilled water. The same solution was used throughout the investigation.

Potassium Iodate, 0.001 Normal: This was made up from the 0.1 Normal solution for every second or third clearance test to check the titre of the sodium thiosulphate.

Potassium Iodide, 5 per cent: This was prepared freshly for each second or third test.

Starch solution, 1 per cent: This was made freshly about once a week.

Procedure.

Precipitation.

Plasma: 2 cc of plasma were diluted with 10 cc distilled water, after which 16 cc of the acid zinc sulphate solution and 2 cc 0.75 normal sodium hydroxide were added. After vigorous shaking the flasks were allowed to stand 30—40 minutes before filtration.

Urine: The standard Somogyi precipitation without previous addition of water was used. Before precipitation the urine was first diluted 20—100 times according to the urine flow and the expected clearance level.

Oxidation.

Each sample was pipetted into a 125 cc Erlenmeyer flask. About 5 cc of water were added to the ten cc aliquots. To each sample three drops of phosphoric acid and then 9—10 drops of the bromine water were added. The flasks were started boiling by hand and then placed on a water bath, where they were immersed in the boiling water to a depth of 0.5—1 cc. The total time of boiling was 15 minutes. The colour and smell of bromine had usually disappeared in 7—8 minutes. Each flask was shaken for a few seconds at least twice while on the water bath. The flasks were then cooled under running tap water.

Titration.

A 2 cc refilling burette, calibrated to 0.01 cc and fitted with a very fine-pointed tip, was used. Before each day's titration 10—20 cc of the thiosulphate solution were run through the burette. The 5 per cent potassium iodide solution was added to each sample just before titration. Titration was carried to a point where the yellow colour began to be somewhat difficult to detect, after which the 1 per cent starch solution was added. After this the titration was carried out rather slowly until the flask containing the

sample and that containing distilled water were indistinguishable. The titration was carried out against a background of white paper, while the source of light was a frosted bulb attached to a movable holder, which could be easily adjusted so that no shadows were thrown.

After a fair number of trials had been made with a 0.001 normal thiosulphate solution, this was replaced by a 0.002 normal, which according to the author's impression gave a more readily determined end-point.

For calculations and the technique of determining the exact titre of the 0.002 normal thiosulphate solution reference may be made to Alpert's paper.

Recoveries of Diodrast-Iodine from Plasma and Urine.

In urine diluted 15 to 150 times no blank was found. In close agreement with the observations of Earle, Taggart and Shannon and in some contrast to the statement of Alpert the plasma was found mostly to contain a measurable blank by the above-described procedure. Generally it amounted only to one or two drops of the thiosulphate solution, but on isolated occasions blanks between 0.10 and 0.20 mg per 100 cc were found. As this blank would tend to balance losses of diodrast-iodine occurring at the levels generally encountered, the author has followed the example of Earle, Taggart and Shannon in not introducing a correction for the blank.

Table 4. Statistical Analysis of Recoveries of Diodrast-Iodine.

Known Diodrast-Iodine concentr. Mg per 100 cc	Number of observations	Mean dev. of determined fr. known values Per cent	Standard dev. of the indiv observations Per cent	Standard dev. of the mean Per cent
Plasma				
0.84	21	0	3.8	0.84
1.25	18	+2.2	1.6	0.4
1.67	18	+0.36	2.15	0.53
1.97	19	+2.9	2.4	0.58
3.94	24	-2.3	1.48	0.285
Urine				
1.25	17	+2.9	2.4	0.59
2.95	16	+2.4	2.3	0.61
4.92	25	-0.77	2.4	0.45
6.25	20	-4.5	2.6	0.59

These values compare rather well with those given by Alpert, although the dispersion may appear somewhat wider. The tendency to low values in the upper range of concentrations (4—6 mg per 100 cc) seems to be about the same as that found by Alpert as well as Earle, Taggart and Shannon.

Duplicate analyses were always performed.

Inulin

Inulin was analysed principally by the methods of Corcoran and Page (1939) and Alving, Rubin and Miller (1939). In the yeasting procedure the technique of Hogeman was closely followed, while the stage of boiling and colour development was performed in a closed system of the type used by Laake (1945).

Reagents.

ZnSO₄, 7 H₂O. 10 per cent.

NaOH. 1.1 Normal.

Diphenylamine (Merck).

HCl (conc.).

Ethyl alcohol. 96 per cent.

The acid diphenylamine reagent was made up freshly for every test. Of a 20 per cent diphenylamine solution in absolute alcohol 12 cc were added to a mixture of 140 cc of 96 per cent ethyl alcohol and 100 cc of concentrated HCl.

Yeasting. Normal and diabetic plasmas and diabetic urines were yeasted according to the procedure of Corcoran and Page (1939) and Hogeman (1948). Ordinary baker's yeast was washed five times in distilled water (5 gm to 10 cc water). Of this suspension 0.4 cc was centrifuged rapidly for 8—10 minutes. The tubes were left standing upside down for about 30 minutes, whereupon the inside of the tubes was dried with filter paper. Six cc of plasma were added, the yeast stirred up and the tubes left at 38° for 45 minutes, whereupon they were again centrifuged.

Precipitation. To 4 cc of plasma 6 cc of 10 per cent zinc sulphate solution and 2 cc of 1.1 N NaOH were added. After thorough shaking for about 10 minutes, the mixture was centrifuged for 10 minutes, whereupon the clear, supernatant fluid was pipetted off.

Hydrolysing and Development of Colour. Of the sample 2 cc were added to 3 cc of the diphenylamine reagent and the volume made up to 15 cc with 96 per cent alcohol in a graduated Jena tube. The metal tube-stand was provided with metal plates, which could be firmly screwed down on the rubber stoppers. The use of rubber stoppers never caused any disturbing opalescence, in agreement with the results of Röjel (1942) and Laake (1945) but contrary to those of Hogeman (1948).

The tubes were left standing in boiling water for 30 minutes, whereupon they were rapidly cooled in running tap water. The colour was then as soon as possible read in a Dubosq's colorimeter against a 10 mg per cent inulin standard.

The standard curve was drawn from 100 observations on inulin solutions of closely spaced concentrations from 5 to 30 mg per 100 cc. The 10 mg per cent inulin standard was made up afresh every month. Plasma inulin concentrations ranged from 20 to 60 mg per 100 cc. With the $\frac{1}{2}$ dilution introduced during the precipitation they thus fell in the middle part of the curve. When the concentrations arrived at after the dilution of urine chanced to lie outside or near the ends of the curve, the determination was repeated.

Yeasted plasma blanks varied between 0.2 and 0.7 mg per 100 cc, exceptionally rising above 1 mg per 100 cc.

Urine and yeasted plasma recoveries at concentrations between 15 and 60 mg per 100 cc ranged from 96 to 103 per cent, with extreme isolated observations of 91 and 109 per cent. Towards the end of the investigation, when a photo-electric colorimeter was available, the reading accuracy could be definitely increased.

Determinations were always made in duplicate, which proved a fairly close check.

During the course of the investigation the methods were re-checked a couple of times by making a series of recoveries. These showed somewhat less scattering than in the early work with the methods.

Plasma concentrations of inulin and diodrast were plotted on a semilogarithmic graph on the logarithmic coordinate against time on the linear. The

concentrations for individual periods were arrived at by interpolation, using the point two and a half minutes before the midpoint of the period. Ordinary clearance calculations were applied. All clearance values were corrected to 1.73 sq. m.

The Material.

The normal control material was composed of predominantly rather young patients in good shape, in convalescence after febrile diseases, undergoing neurological observation, suffering from disease of the skin or in a couple of cases from early diabetes. Admittedly, from a renal point of view, these "normals" could not be regarded as a sufficiently pure material for establishing normal parameters, but they were considered to be free enough from suspicion of organic vascular kidney disease to act as controls from the specific point of view adopted in this investigation. Carbon-dioxide inhalation was applied to twenty-two cases examined with the continuous infusion clearance technique. Of these, two cases were excluded because of pyrogenic reactions, as previously mentioned. In one case the carbon-dioxide inhalation had to be abandoned because of a persistent hiccup, in another the experiment was disrupted because of nervousness and lack of cooperation. Thus, there remain observations in 18 cases.

The series of hypertensives studied with the continuous infusion technique during inhalation of CO_2 numbered 52 cases. As previously explained, three cases were excluded because of unfavourable cardiac response. In three further cases there were observations made only after bilateral sympathectomy. These were excluded from the main series and will be discussed in connection with the subjects examined pre- and post-operatively. There remain 51 observations on 46 subjects. Observations made on the same individual have been recorded separately, unless otherwise stated. This material is naturally not considered to be fully representative of all stages and varieties of essential hypertension. The severe shortage of hospital beds prohibited the admission for study of quite a number of early cases with slight symptoms. On the other hand, the stress resulting from the CO_2 inhalation was not inconsiderable, and hence it was necessary to exclude from the study all cases with advanced cardiac disease. Possibly this is one contributory explanation of the predominance of females in the material, as males with advanced hypertensive disease without serious cardiac involvement appeared scarce.

Care was taken to exclude cases in which there was any suspicion of a chronic glomerulonephritis as the cause of the hypertensive process. In one case (V.F.B., a male of 54 years) a diagnosis was initially made of chronic glomerulonephritis, probably

partly because of the coexistence of a subacute polyarthrititis with scleritis. However, further study revealed that this patient had two brothers with considerable elevations of blood pressures (in one ranging from 250 to 300 mm Hg, in the other from 200 to 250 systolically). Furthermore, for three years before and two years after the renal functional study this patient showed blood pressures ranging from 260 to 290 systolically with no or inconsistent proteinuria. At the time of the renal study the blood values were entirely within normal limits, and the maximal concentrating capacity was fully normal. The basal values showed a markedly reduced diodrast clearance with a moderate reduction of the inulin clearance, giving a filtration fraction of 0.30. This renal functional pattern together with the other clinical characteristics seemed conclusive enough to warrant a change of the diagnosis to essential hypertension.

In one female, 49 years old, there had been repeated attacks diagnosed as cystopyelitis 13 years prior to the renal study. Since she now presented none of the symptoms of chronic pyelonephritis thoroughly discussed by Raaschou (1948, p. 44 *et seq.*) and showed a normal intravenous pyelogram, she was included in the series.

A few of the patients in the study presented a not fully constant elevation of the blood pressure to clearly pathologic values. The criterion for including them was that they should on at least two separate occasions under satisfactory conditions show a blood pressure of more than 160/100 mm of mercury, although a couple of them showed a pressure within the normal range at the actual time of the renal study.

The blood pressure measurements used in this study were made by a few highly trained observers. Measurements during the clearance procedure were made by the author himself. For the diastolic pressure that point was taken at which the sounds change character, although it appears from Steele's comparison of direct intra-arterial manometry and the auscultatory method as if the point of disappearance of sound would more closely approximate the true diastolic level (quot. from Goldring and Chasis, 1944).

The routine clinical work-up included cardiac x-rays, electrocardiography and one or several funduscopic examinations by an expert ophthalmologist. Repeated urine analyses were made. The non-protein nitrogen was usually determined at least twice. In the great majority of cases at least one test was made for maximal concentrating capacity and in some of the patients one or more Rehberg's creatinine clearance tests were performed.

All cases in which sympathectomy was contemplated were subjected to one or repeated amytal tests and cold pressor tests.

Intravenous pyelography was used on 30 patients, predominantly in the younger age-groups or when there were any doubts of the diagnosis of essential hypertension. Some of the pyelographed cases seem worthy of comment.

In a male of 33 years, E.L.J., a growing stone had been found in the left pelvis, and left pyelolithotomy had been performed one month before the renal study. In a female

of 40 years, T.S., the left renal pelvis contained some small concretions that produced no symptoms. In the case of M.A., a female of 48 years, there was found a rather large hydronephrosis on the right side with normal conditions on the left side. Since this case fulfilled the requirements for the diagnosis in other respects, it was included in the series of hypertensives, although with some doubt as to justification.

In a male of 42 years, G.H.A., there was found on two occasions very much less density in renal contrast on the left side. An attempt to determine the function of the separate kidneys was not successful, in so far as the catheter could not be passed up into the right ureter. However, from the left side, where the density of the pyelographic shadow had been very poor, urine was obtained in intermittent, rhythmic flow, the Cd on this side averaging 235 cc/min. The observation of a rather well maintained renal function on the side giving a very poor pyelographic shadow seems in line with the observations of Chasis and Redish (1942), who found significant variations in the relative densities of pyelographic shadows in hypertensive patients with kidneys of equal functional capacities. As only this unilateral study was made, the case has naturally been excluded.

Nine observations on six subjects were performed after bilateral sympathectomy (2 of Peet's modification, 4 of Smithwick's). Owing to the failure to get a blood sample during the CO₂ inhalation, the observation during the CO₂ period had to be discarded in one case.

A series of twenty cases of miscellaneous kidney disorders were submitted to the same procedure. This series includes measurements on two cases of essential hypertension, where a co-existing state, which could probably affect the renal function, was present, and therefore it was considered safest to keep these cases out of the group of essential hypertensives.

A series of 29 cases, including normals, hypertensives and miscellaneous kidney disorders, were submitted to the single intravenous injection technique before the unsuitability of this method for the purpose was established. This series will be shortly discussed separately.

CHAPTER IV.

Effect of CO₂ on Renal Function in Normals.

The effect of inhalation of CO₂ on the renal function in the control group is shown below in Table 5, and is further to be seen in connection with the series of hypertensives in the graphs on pages 41 and 42.

Table 5. Effect of Inhalation of CO₂ on Clearances of Inulin and Diodrast in Normals.

Age	Diagnosis	C _{In}			C _D			FF	
		Basal	CO ₂	Per cent change	Basal	CO ₂	Per cent change	Basal	CO ₂
Males									
23	Pneumonia								
	convalesc.	—	—	—	524	375	—29	—	—
35	Sexual neurosis...	—	—	—	475	428	—5	—	—
19	Orthost. hypotens.	—	—	—	501	457	—9	—	—
34	Diabetes mell. ...	167	136	—19	769	468	—39	0.20	0.29
21	Reiters disease ...	98	76	—23	800	580	—28	0.12	0.13
17	Orthost. hypotens.	147	96	—34	790	550	—30	0.18	0.19
15	Diabetes mell. ...	175	139	—21	1000	730	—27	0.18	0.19
	Average	147	111	—25	694	513	—26	0.17	0.20
Females									
43	Neurol. observ. ...	—	—	—	437	302	—31	—	—
35	Neurol. observ. ...	—	—	—	625	425	—32	—	—
32	Neurol. observ. ...	—	—	—	618	492	—20	—	—
30	Multiple scler. ...	—	—	—	505	487	—4	—	—
53	Thyreotoxicosis ...	—	—	—	581	448	—23	—	—
51	Thyreotoxicosis ...	87	95	+9	639	535	—16	0.14	0.18
30	Neurosis	133	119	—11	608	533	—12	0.22	0.22
23	Hysteria	84	63	—25	514	330	—36	0.17	0.19
17	Lupus erythem.								
	dissem. acut.	114	77	—32	643	453	—30	0.18	0.18
19	Sarcoma	107	105	—2	630	525	—15	0.17	0.20
19	Dermatitis								
	herpetiform.	145	112	—23	762	515	—32	0.19	0.22
	Average	111	95	—14.5	595	458	—23	0.18	0.20
	Average.								
	Both sexes.	125	101	—19	634	478	—23	0.18	0.20

Of the cases presented in Table 5, the case of lupus erythematosus disseminatus acutus showed a rather constant proteinuria. The patient was in good shape at the time of the renal study, and at the post mortem examination about two years later there was not found the specific glomerular changes stated to occur in this disease. With one exception all clearances fell under the action of CO₂. The case showing a small increase in C_m was a 51 years old female in a moderately severe thyreotoxic state with blood

pressures ranging from 150/90 to 185/100. As there was no definite evidence of vascular disease, this case was included among the normals.

As is seen from the table, all the cases with clearances at or above the mean normal level show rather large decreases, especially in C_D , while the response seems more variable in the cases with initially low values, the three decreases of less than 10 per cent occurring in these cases.

The 23 per cent reduction in C_D under the action of CO_2 seems somewhat less than the decreases reported in the dog from the thermostromuhr studies of the Rein school. Comments on this seem difficult, as the two methods of measurement are not strictly comparable.

The average reduction of C_M , 19 per cent, appears to be of the same order of magnitude as that found by Brun, Raaschou and Knudsen in the one hour 60° tilting test.

The slight increase in the filtration fraction may or may not be significant, but is anyhow definitely less than the change produced by adrenalin (Smith, 1943).

As the decrease in C_D occurred against a mean pressure rise of 15 mm, the increase in renal vascular resistance should be considerable, assuming for the present that the drop in C_D is due exclusively to the vascular action of CO_2 . By adopting the formula advanced by Lauson, Cournand and Bradley (1944) an attempt was made to get an approximative impression of the increase in renal vascular resistance.

$$R_k = \frac{\text{mean arterial pressure} - \text{renal venous pressure}}{\text{renal blood flow}}$$

As the renal venous pressure is small as compared with the mean arterial, it was set at zero by Lauson *et al.*

The mean arterial pressure is represented in this study by the mean of the systolic and diastolic pressures.

To facilitate comparison with the figures given by the above authors the effective renal plasma flow has been calculated from the hematocrit and the C_D . In those cases where no hematocrit determination had been made the normal average of 43 per cent has been used. This of course introduces a further error in the calculation of the absolute values of the renal resistance, but should not affect the change in resistance due to CO_2 in the individual case. For the same reasons of comparison the mean pressure is converted into dynes per cm^2 by the factor 1332 and the blood flow expressed in cc per second.

Calculated in this way, the normal vascular resistance of the kidney was found by Lauson, Cournand and Bradley to vary between 4000 and 10000 units in normals. In the present series the values ranged from 4500 to 12000 units in 18 normal subjects, only two values (10850 and 12000) exceeding 10000. The calculated increase in renal resistance caused by CO_2 varied between 20 and 98 per cent, the average being 57 %. This figure is naturally regarded with strong reservation, but is thought to give some impression of the magnitude of the increase in renal vascular resistance.

Effect of CO₂ on Renal Function in Essential Hypertension.

The response to CO₂ will be discussed in relation to level of renal clearances, age and extrarenal features of the hypertensive process. The effect of sympathectomy, the variability of the blood pressure in relation to renal function and the occurrence of other signs of disturbed renal function will be discussed under separate headings.

In Table 6 all the hypertensive subjects unoperated upon have been arranged according to the level of the diodrast clearance.

Table 6. Effect of CO₂ on Renal Clearances in Essential Hypertension.

Patient	Age	Sex	CD			C _{In}			FF	
			Basal	CO ₂	Per cent change	Basal	CO ₂	Per cent change	Basal	CO ₂
E. E.	21	m	610	515	-16	159	143	-10	0.24	0.26
G. W.	46	f	583	516	-11	106	109	+3	0.19	0.21
I. J.	53	m	506	454	-14	134	134	0	0.26	0.29
E. L. J. ...	34	m	500	430	-14	108	105	-3	0.22	0.24
» ...	34	m	422	380	-10	86	95	+10	0.20	0.24
S. P.	48	f	488	434	-11	—	—	—	—	—
S. S.	38	m	484	450	-7	93	85	-9	0.19	0.19
T. E. A. ...	46	m	469	370	-23	102	67	-34	0.21	0.18
» ...	46	m	430	375	-13	98	102	+4	0.23	0.28
H. O.	49	f	465	282	-40	86	64	-25	0.19	0.20
T. C.	47	m	461	372	-19	84	76	-10	0.18	0.20
K. B.	56	m	450	334	-26	122	125	+3	0.25	0.34
E. B.	33	m	439	362	-17	153	133	-13	0.34	0.33
E. A.	48	f	438	382	-13	112	101	-10	0.25	0.27
H. J.	53	m	435	348	-20	101	103	+2	0.23	0.30
O. H.	59	m	432	356	-18	—	—	—	—	—
A. P.	49	m	420	352	-16	98	112	+12	0.23	0.32
B. H.	62	f	417	450	+8	115	127	+10	0.28	0.28
J. O. P. ...	50	m	411	475	+15	101	143	+42	0.22	0.26
E. P.	49	f	410	374	-9	—	—	—	—	—
S. L.	42	f	407	338	-17	112	104	-7	0.27	0.31
S. S.	49	f	407	409	0	94	94	0	0.23	0.23
» ...	49	f	337	387	+15	69	104	+50	0.21	0.27
A. L.	48	f	400	376	-6	93	92	-1	0.23	0.25
» ...	48	f	331	320	-3	99	105	+6	0.29	0.32
A. D.	51	f	397	370	-7	85	91	+7	0.22	0.25
E. L. W. ...	46	m	386	322	-17	103	77	-25	0.27	0.24
T. S.	40	f	380	222	-41	107	82	-27	0.28	0.37
H. A.	67	f	376	427	+14	94	94	0	0.25	0.22
S. N.	60	f	376	324	-13	72	72	0	0.20	0.22
B. G. E. ...	25	m	375	366	-3	86	87	+1	0.22	0.24
» ...	25	m	335	372	-19	—	—	—	—	—
K. W.	46	f	367	340	-8	96	96	0	0.26	0.28
E. P.	52	f	367	381	+4	80	91	+14	0.22	0.24
H. P.	47	f	356	242	-30	92	80	-13	0.26	0.33
M. A. O. ...	47	f	354	336	-5	81	78	-3	0.23	0.23
M. L.	35	f	352	286	-19	—	—	—	—	—
E. M.	52	f	347	360	+4	92	99	+8	0.27	0.28
A. S.	46	f	346	330	-5	76	95	+25	0.22	0.29

Table 6 (continued).

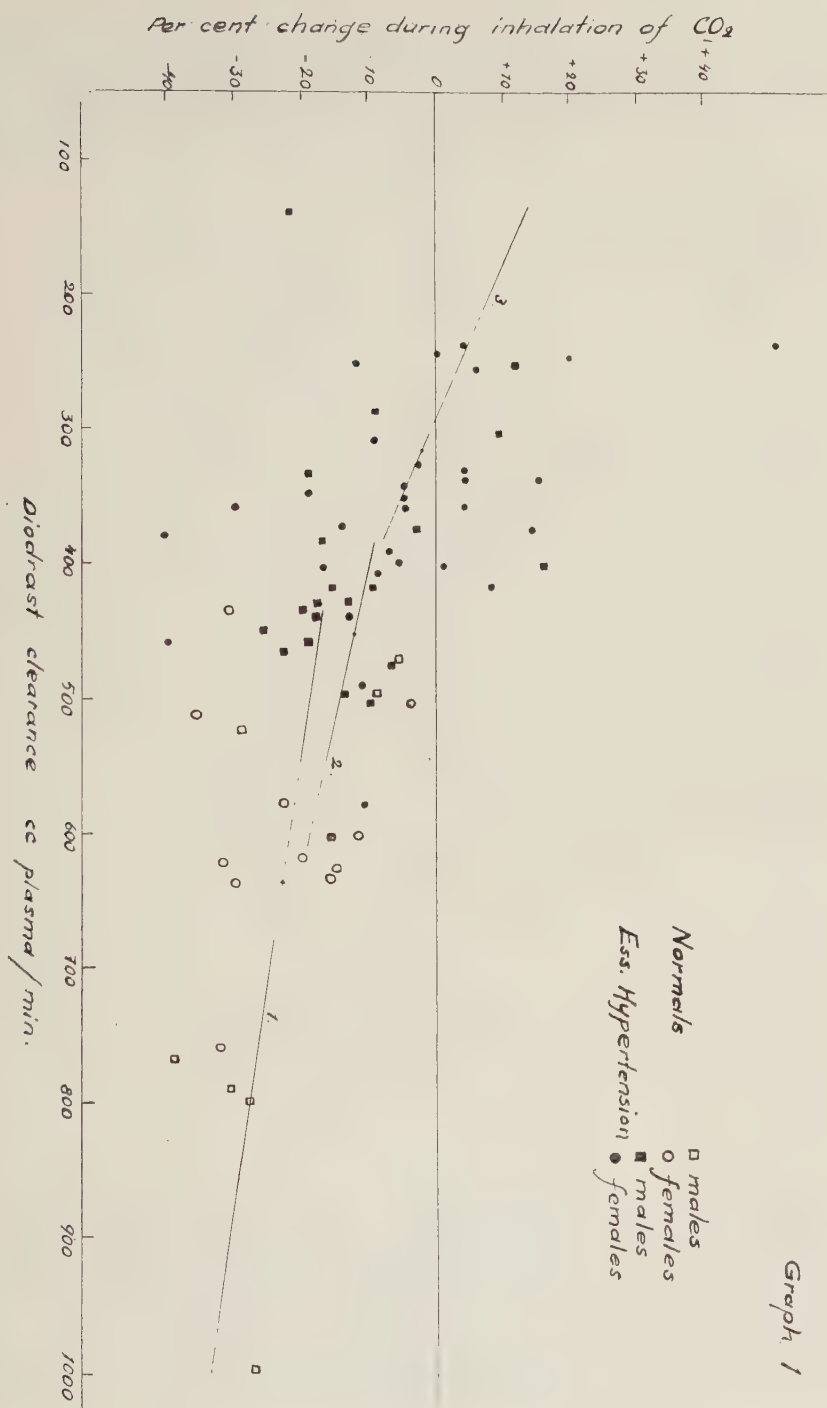
Patient	Age	Sex	C _D			C _{In}			FF	
			Basal	CO ₂	Per cent change	Basal	CO ₂	Per cent change	Basal	CO ₂
H. J.	42	f	340	355	+4	92	85	-8	0.27	0.24
O. J.	55	f	310	282	-9	58	56	-3	0.20	0.21
A. H.	57	f	308	327	+6	65	71	+9	0.21	0.21
E. S.	42	m	304	332	+9	70	75	+7	0.23	0.23
E. N.	48	m	286	261	-9	72	80	+11	0.25	0.31
E. A.	53	f	256	225	-12	80	78	-2	0.32	0.34
V. B.	54	m	255	286	+12	77	82	+7	0.30	0.29
T. B.	52	f	250	300	+20	63	80	+27	0.25	0.27
J. S.	52	f	246	247	0	66	65	-1	0.27	0.26
A. B.	52	f	242	365	+51	55	114	+107	0.23	0.30
M. A.	48	f	241	248	+4	63	71	+13	0.26	0.29
K. J.	37	m	137	107	-22	38	37	-3	0.28	0.34

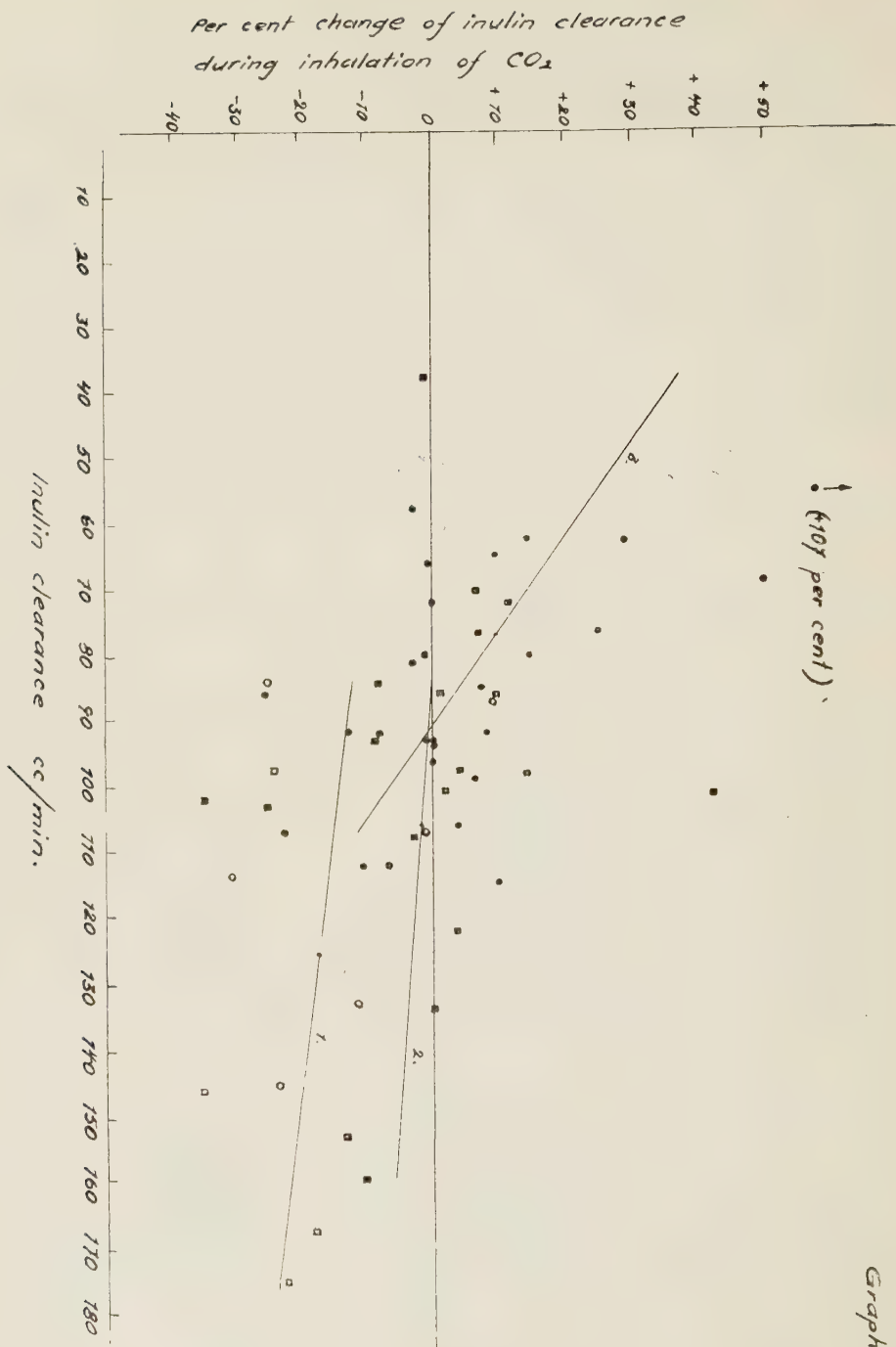
A visual impression of the observations tabulated above is to be gained from Graphs 1, 2, 3, 4 and 5.

Change of Renal Clearances under the Action of CO₂ in Relation to Level of Renal Function.

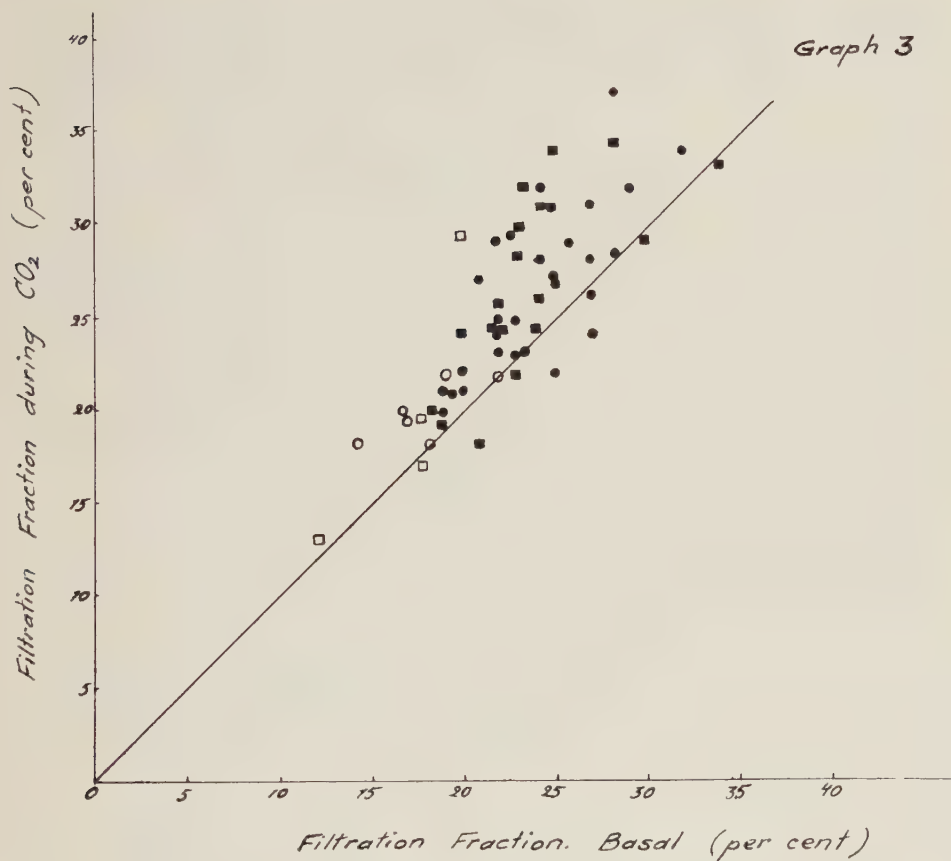
For purposes of easier demonstration the observed changes in clearances have been converted into percentage deviations and presented as such in the following graphs. In graphs 1 and 2 the responses to CO₂ at various levels of C_D and C_{In} are shown. The material of hypertensives has been divided into two equally large groups according to the level of C_D, the borderline becoming 380 cc/min. This naturally gave a certain overlapping between the groups in the case of C_{In}. The lines have been computed by the method of least squares, their length being confined exactly to the range of the underlying experimental observations. The points on the lines denote the averages of the respective groups. Line 1 represents normals, line 2 hypertensives with moderate reduction of renal function and line 3 hypertensives with severe such reduction.

The tendency to a rise of renal function following the administration of CO₂ in the low range of clearances is clearly seen. This tendency is seen to be more outspoken in the case of the inulin clearance, where not in a single instance does there occur a significant fall under the action of CO₂ below a clearance of 80 cc/min. The isolated point below to the left in Graph 1 at a C_D of 137 cc/min. represents a case of extremely malignant hypertension in a male of 37 years.





In the individual case there is usually the same type of response in both clearances. This is evident from Table 6 and is further shown in Graph 3, which illustrates the practically uniform although rather moderate rise in filtration fraction under the action of CO_2 .



It could possibly be argued that the more pronounced rise in filtration in the low clearance range and the ensuing rise of the amount of filtered diodrast would be capable of explaining the observed rise in C_D . In Table 7 the calculated amounts of filtered and tubularly excreted diodrast are given during control periods as well as under the action of CO_2 . In the expression $C_{In} \cdot P_D \cdot FW$ in this table, the value of 0.72 has been used for FW (Goldring, Chasis, Ranges and Smith, 1940).

Table 7. Changes in Filtered and Tubularly excreted Diodrast under the Action of CO₂ in Cases with Rise in Cd.

Pat.	Per cent change of clearance		P _D		U. V		C _{In} . P _D . FW		T _D	
	C _D	C _{In}	Basal	CO ₂	Basal	CO ₂	Basal	CO ₂	Basal	CO ₂
A. B.	+51	+107	1.60	1.60	4.20	6.40	0.69	1.44	3.51	4.96
A. H.	+6	+9	2.56	2.64	8.10	8.96	1.20	1.34	6.9	7.62
H. A.	+14	+0	1.90	1.90	7.25	8.15	1.29	1.29	5.96	6.86
J. P.	+16	+42	1.15	0.96	5.38	5.30	0.84	0.99	4.54	4.31
M. A.	+4	+13	2.35	2.26	5.62	5.60	1.06	1.14	4.56	4.46
V. B.	+12	+7	2.00	2.00	5.53	6.35	1.24	1.31	4.29	5.04
E. P.	+4	+12	1.80	1.78	6.17	6.40	0.98	1.10	5.19	5.30
T. B.	+20	+28	2.00	2.20	4.96	7.40	0.91	1.27	3.95	6.13
E. M.	+4	+8	2.05	2.26	6.71	7.67	1.28	1.51	5.43	6.16
S. S.	+0.5	+0	1.64	1.68	6.60	6.85	1.14	1.14	5.46	5.71
S. S.	+15	+50	2.40	2.26	8.00	8.72	1.17	1.73	6.83	6.99
E. S.	+9	+7	1.32	1.22	4.23	4.25	0.71	0.66	3.52	3.59
I. S.	+0	-1	2.13	2.20	5.93	6.10	1.15	1.15	4.78	4.95
H. J.	+4	-8	1.63	1.74	5.97	6.73	1.14	1.12	4.83	5.61
B. H.	+8	+10	1.90	2.23	7.18	9.18	1.53	1.96	5.65	7.22

In cases showing no or only a negligible change in the plasma diodrast level there is seen to occur a consistent increase in T_D in those cases in which the diodrast clearance rose. Even in some of the cases showing a small decrease of P_D there was seen some increase in T_D.

Still, it is conceivable that the administration of CO₂ might affect the binding of diodrast to the plasma proteins and thus change the proportion

Table 8.

	Normals	Essential Hypertension All cases	Essential Hypertension C _D 610-380 cc/min	Essential Hypertension C _D 380-137 cc/min.
I. Diodrast clearance				
r.	0.83	0.60	0.64	0.71
M _x (basal)	634.5±3×32.8	381.2±3×12.4	450.7±3×10.8	314.4±3×11.4
M _{yx} (CO ₂)	479.6±3×22.2	348.1±3×10.6	393.0±3×11.5	308.8±3×12.5
Equation of regression line	y=0.565x+121.1	y=0.666x+94.1	y=0.690x+81.6	y=0.773x+65.7
II. Inulin clearance				
r.	0.84	0.75	0.73	0.52
M _x (basal)	125.7±3×9.8	91.1±3×3.4	106.6±3×4.2	76.8±3×3.2
M _{yx} (CO ₂)	101.8±3×7.6	92.6±3×3.3	103.7±3×4.8	82.4±3×3.3
Equation of regression line	y=0.659x+18.88	y=0.715x+27.41	y=0.833x+14.84	y=0.541x+40.85

All regression coefficients significant, using the 0.01 level of significance.

between filtered and tubularly excreted diodrast. This possibility has not been subjected to experimental investigation.

It is however concluded that in the majority of cases of a raised diodrast clearance under the action of CO_2 the usually coexistent increase of filtered diodrast is insufficient to account for the increase in the values calculated for C_D .

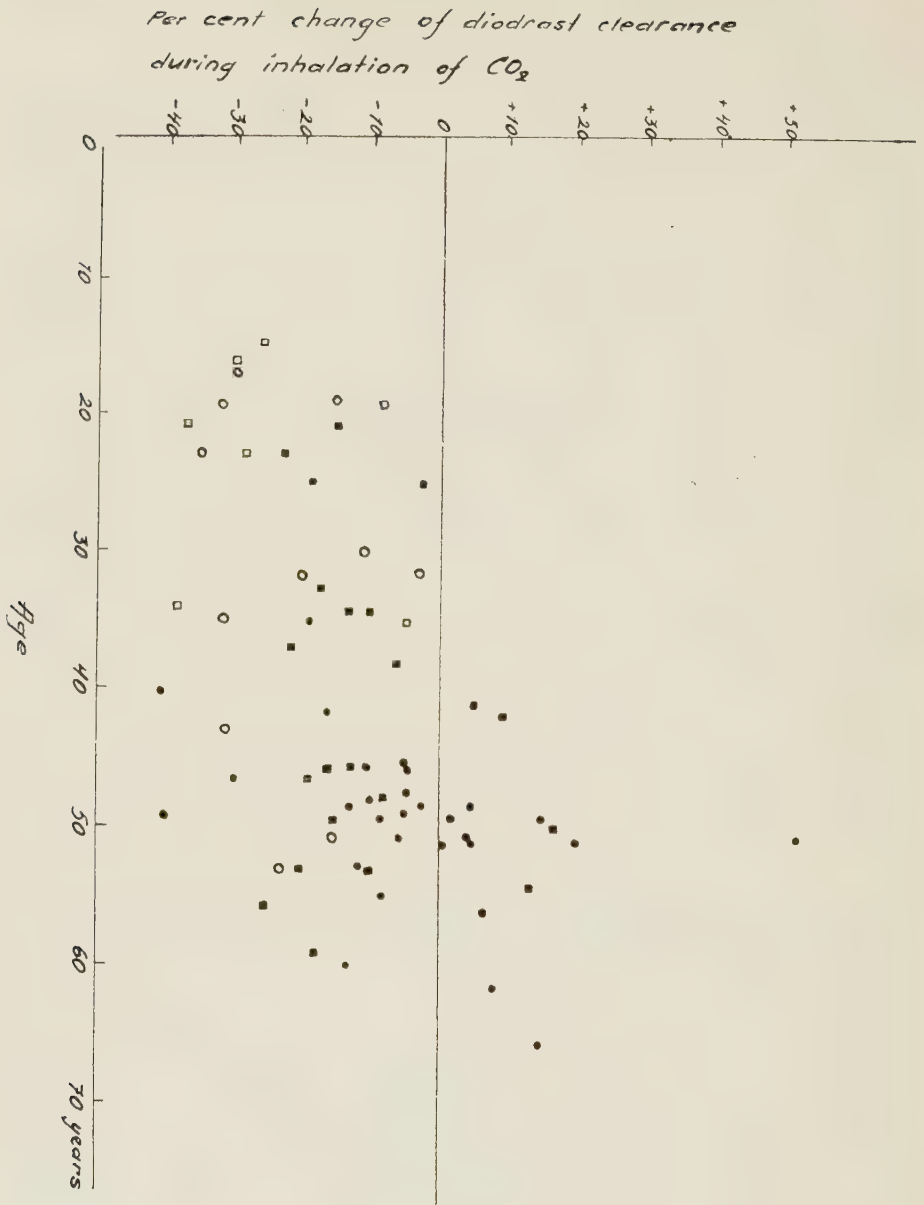
As the use of the percentage deviations in the graphs could be open to question, the means, correlation coefficients and equations for the regression lines computed directly from the experimental observations are given in Table 8. For those interested this should make the drawing of the graphs based directly on the experimentally found values a simple matter.

Influence of Age on the Response to CO_2 of the Renal Clearances in Essential Hypertension.

In Graphs 4 and 5 the cases are arranged according to age irrespective of other characteristics of the hypertensive process. There is seen to be an increasing number of raised values both for C_{In} and C_D in the higher age groups. Below the age of 40 years there occur no rises in C_D whatsoever; while above the age of 50 no single case registered a significant fall in C_{In} under the action of CO_2 . There is however a regrettable lack of data on normal control subjects in the higher age groups.

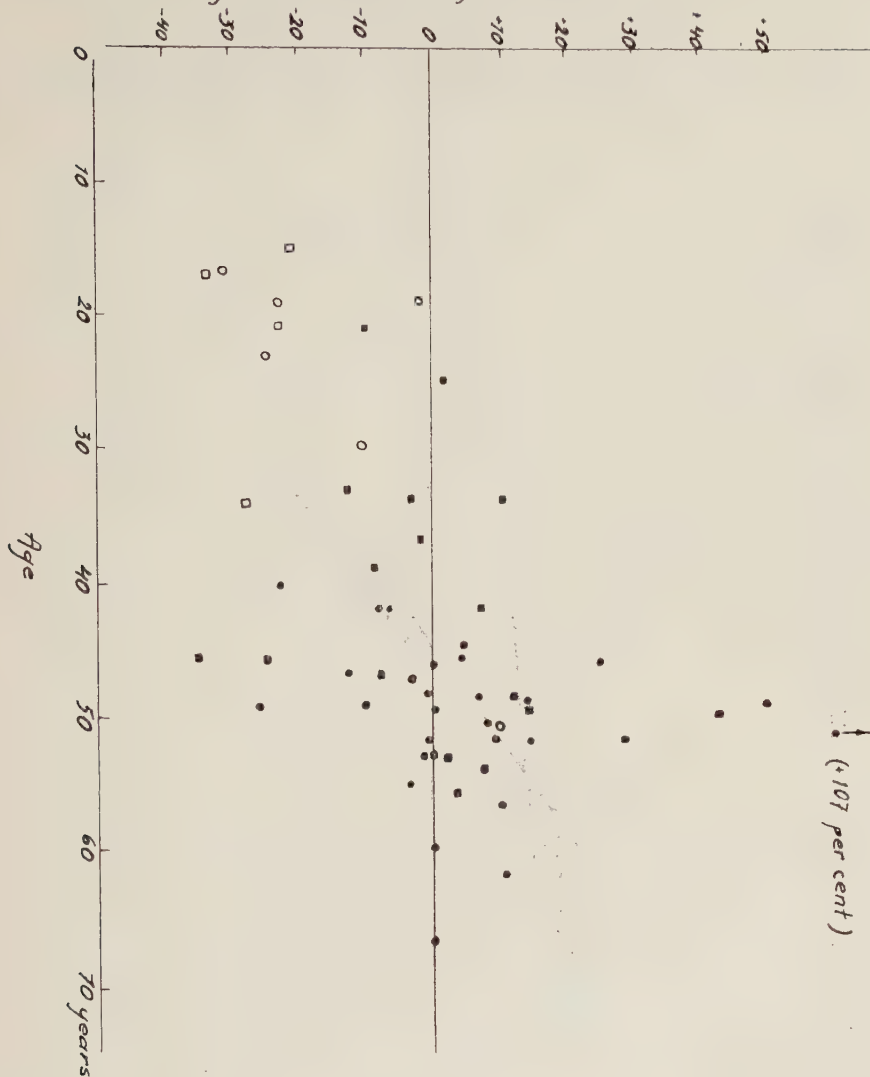
In Graphs 6 and 7 there is submitted an attempt to give a simultaneous impression of the influence of both age and level of renal function on the response to CO_2 . The material of essential hypertension is divided into two as equally large groups as possible. One group, comprising subjects of 49 years or above, embraced 23 observations on C_D and 21 on C_{In} . The other group, with subjects below 49 years, took in 28 observations on C_D and 25 on C_{In} . The lines are computed by the method of least squares and have been drawn exactly as long as there are experimental observations to support them. While the line denoting the change of C_D for subjects below 49 keeps below the zero level at every level of renal function, the line for subjects above 49 is seen to cross the zero line at a C_D of 360 cc/min and to present a rather steep rise. Thus the tendency to inverted response to CO_2 in the subjects above 49 years of age is seen to occur at a higher level of renal function and seems more pronounced than the same phenomenon in the group of cases with low clearances as seen in Graph 1. Approximately the same tendency is seen in the case of C_{In} , the line for the subjects above 49 years intersecting the zero line already at a C_{In} of 115 cc/min as against the line for the subjects below 49, which intersects it at 80 cc/min.

It thus seems as if the combination of high age and low level of renal function would highly favour the occurrence of rises in renal function under the action of CO_2 .



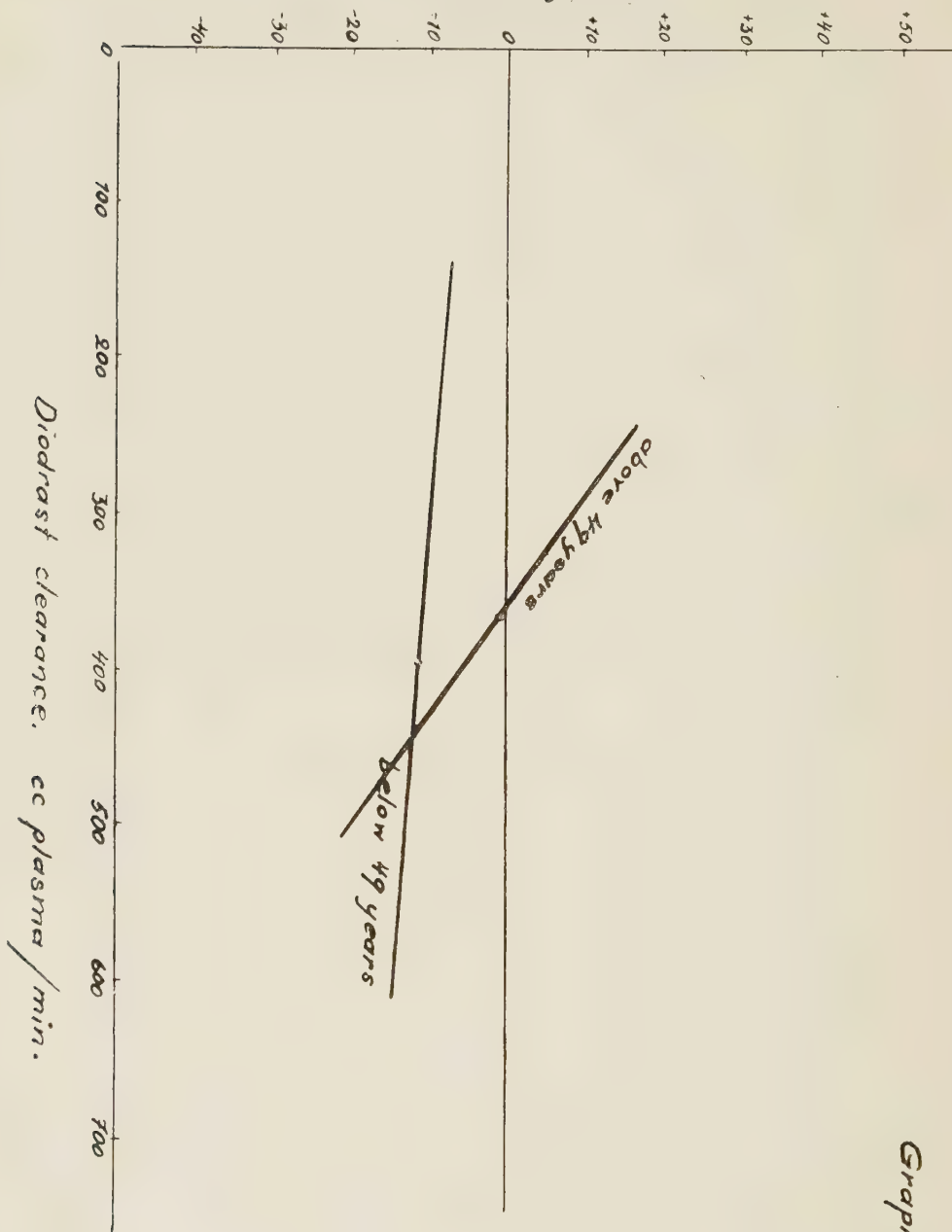
Graph 4

Per cent change of inulin clearance
during inhalation of CO_2



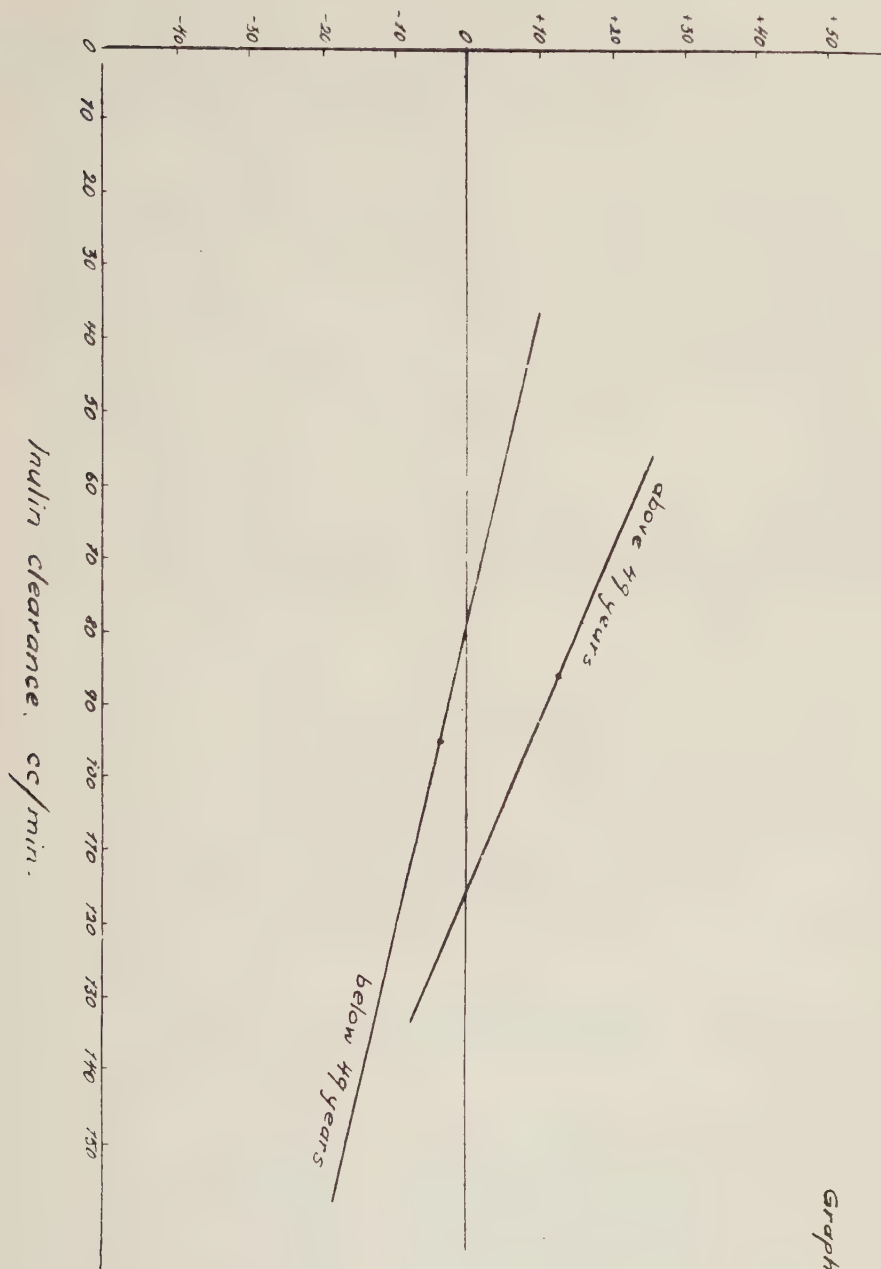
Graph 5

Per cent change of diodrast clearance
during inhalation of CO_2



Graph 6

Per cent change of inulin clearance
during inhalation of CO_2



Graph F

For the same reason as given on page 45 unconverted data for the groups of subjects below and above 49 years are given below.

Table 9.

	Essential hypertension below 49 years	Essential hypertension 49 years and above
I. Diodrast clearance		
<i>r</i>	0.90	0.57
M_x (basal)	$393.6 \pm 3 \times 18.0$	$366.1 \pm 3 \times 15.9$
M_{yx} (CO ₂)	$344.3 \pm 3 \times 15.9$	$352.8 \pm 3 \times 13.2$
Equation of regression line	$y = 0.804x + 27.87$	$y = 0.475x + 179.049$
II. Inulin clearance		
<i>r</i>	0.86	0.71
M_x (basal)	$95.2 \pm 3 \times 4.9$	$86.0 \pm 3 \times 4.6$
M_{xy} (CO ₂)	$90.4 \pm 3 \times 4.2$	$95.2 \pm 3 \times 5.2$
Equation of regression line	$y = 0.735x + 20.422$	$y = 0.815x + 25.080$

The regression coefficient for CI_n in subjects above 49 not significant. The other regression coefficients are significant, using the 0.01 level of significance.

The Effect of Carbon Dioxide on Renal Function in Subdivisions of Essential Hypertension.

An attempt has been made to subdivide the material along the lines suggested by Taylor and Page (1945) and Corcoran, Taylor and Page (1948). The group classified as established essential hypertension has been further subdivided into established hypertension (*a*) without and (*b*) with severe vascular disease. The arbitrariness of this is well recognized. In borderline cases the principle has been to exclude the case from the severe group. Cases with signs of vascular disease predominantly from the heart have likewise not been included in the severe group on the strength of the common occurrence of severe vascular heart disease with no or only slight hypertension.

It should be noted that the group of early hypertension outlined below after the classification of Corcoran, Taylor and Page is early only in the sense that the process has not advanced to the point of producing any definite vascular disease or only very insignificant such. This obviously does not necessarily imply that the cases are early from the point of view of time.

The principles of classification have been as follows.

Early hypertension.

No incapacitation allowed.

Blood pressure: Fluctuating. After bed rest below 160/100.

Brain: No evidence of organic cerebral lesion allowed.

Eyegrounds: Keith O—I.

Heart: No signs of decompensation or x-ray enlargement allowed. E. C. G. No changes or left-axis deviation.

Established hypertension with moderate vascular disease.

Slight to moderate incapacitation allowed.

Blood pressure: Mostly always above 180/110 and only in isolated instances below 160/100 after bed rest.

Brain: No anamnestic or manifest evidence of gross cerebral vascular lesions allowed.

Eyegrounds: Keith I—II.

Heart: Symptoms of slight decompensation or coronary insufficiency allowed. X-ray enlargement and E.C.G. changes allowed.

Arteries: Definite rigidity of temporal and radial arteries not allowed.

Established hypertension with severe vascular disease.

Definite to severe incapacitation.

Blood pressure: Constantly elevated. Levels 320/205—230/125, the diastolic on prolonged bed rest in some instances dropping to 110 mm.

Brain: Cerebral symptoms usually continuously present. Anamnestic or manifest evidence of gross cerebral lesion allowed.

Eyegrounds: Keith II—III—IV.

Heart: Any kinds of symptoms and objective signs allowed within the limits set by the stress of the CO₂ inhalation.

Arteries: Rigidity of temporal and radial arteries allowed.

Arteriosclerotic hypertension.

High age: 67, 62 and 52 years for the three subjects classified as belonging to this group.

Predominantly systolic blood pressure elevation. (Pulse pressure after bed rest more than 1/2 diastolic + 19 mm).

Eyegrounds: Definite vasoconstrictive phenomena not allowed.

Heart: X-ray: Widening and elongation of aortic arch.

Arteries: Rigidity of peripheral arteries.

Malignant hypertension.

Definite and rapidly progressing deterioration.

Brain: In every case classified as belonging to this group there were severe cerebral symptoms as for instance severe vertigo, disorientation, spastic phenomena, adynamia, epileptic seizures or gross cerebral injuries.

Eyegrounds: In three of five subjects Keith IV. Papilledema was not deemed necessary when the general course was definitely malignant and rapidly downhill.

The hazards involved in the above classification seem considerable. Two of the cases classified as early hypertension were accidentally discovered at the age of 46 and 50 years respectively. From the studies of Corcoran, Taylor and Page it appears that these might just as well be cases of incipient arteriosclerotic hypertension.

The most difficult problem, however, seemed to be whether a case should be included in the group of established hypertension with severe vascular disease or not. The case

of S.L., a female of 41 years, serves to illustrate this. The patient presented a history dating back 3—4 years. Her subjective symptoms were slight transitory dizziness and moderate breathlessness and tachycardia on exertion. Blood pressures ranged between

Table 10. Effect of Carbon Dioxide on Renal Function in Normals and Subdivisions of Hypertensive Disease.

	Number of subjects	CD			Number of subjects	C _{In}			FF	
		Basal	CO ₂	Per cent change		Basal	CO ₂	Per cent change	Basal	CO ₂
Normals										
Males.....	7	694	513	—26	4	147	111	—25	0.17	0.21
Females.....	11	595	458	—23	6	111	95	—14.5	0.18	0.20
Total	18	634	478	—23	19	125	102	—19	0.17	0.20
Essential Hypertension										
Early Hypertension										
Males.....	6	472	422	—11	6	109	109	+0	0.23	0.26
Females.....	3	465	362	—22	2	96	86	—10.5	0.19	0.21
Total	9	469	402	—14	8	105	103	—2	0.22	0.25
Established Hypertension										
Males.....	9	434	371	—14.5	9	108	104	—4	0.25	0.28
Females.....	15	381	351	—8	13	88	93	+6	0.24	0.27
Total	24	397	356	—10	22	96	97	+1	0.24	0.28
Established Hypertension with severe Vascular Disease										
Males.....	2	280	309	+14	2	74	79	+7	0.26	0.26
Females.....	8	283	286	+1	8	74	81	+9	0.26	0.28
Total	10	282	293	+3	10	74	80	+9	0.26	0.26
Malignant Hypertension										
Males.....	5	348	295	—15	5	68	65	—4	0.23	0.25
Females.....	1	354	346	—2	1	81	78	—2	0.23	0.23
Total	6	349	302	—13	6	71	69	—3	0.23	0.24
Arteriosclerotic Hypertension										
Males.....	—	—	—	—	—	—	—	—		
Females.....	3	383	419	+9	3	96	104	+8	0.25	0.25
Total	3	383	419	+9	3	96	104	+8	0.25	0.25
Sympathectomized Hypertension										
Males.....	2	308	324	+5	2	56	71	+27	0.18	0.22
Females.....	6	478	459	—4	4	93	104	+12	0.20	0.23
Total	8	435	410	—6	6	81	93	+15	0.20	0.23

310/170 and 255/140. There was moderate left ventricular enlargement. E.C.G. showed left-axis deviation with depressed S-T segments in leads I and II, an inverted T_1 and a biphasic T_2 . Eyegrounds were classified as Keith III, the most conspicuous feature being that the arteries for long stretches were sheathed. There was considerable doubt as to the group in which the patient should be placed. A one year follow-up after bilateral lumbodorsal sympathectomy showed complete freedom of subjective symptoms and blood pressures between 210/110 and 170/120. There was no definite change in the heart x-ray. The E.C.G. was normalized and there was a very definite improvement in the eyegrounds with a disappearance of the sheaths along the arteries. The patient was transferred from the severe to the less severe group, since it was considered that the evidence for advanced organic vascular disease having been present was not sufficient.

In some cases with extreme elevations of blood pressure (270/170—320/200) of long standing and presenting definite symptoms from one or more organs for several years there was registered a blurring of the margins of the disc alongside with definite retinal arteriolar changes. These cases were not grouped as malignant, as it was thought that from the point of view of vascular changes they should have more in common with the cases classified as established hypertension with severe vascular disease. This point may of course be debatable.

As is seen in Table 10, there seems to be a decreasing tendency for the clearances to drop under the action of CO_2 in groups with the more advanced vascular disease. A slight tendency to increase during CO_2 administration is seen in the group of established hypertension with severe vascular disease. The response in the three cases classified as arteriosclerotic hypertension was in every case a slight increase. In sympathectomized hypertension the fall in C_D under CO_2 is seen to be small and less than in the groups with a comparable level of basal C_D . The increase in C_{in} due to CO_2 would seem significant in this group.

There is a frequent occurrence of an abolished or inverted response of the clearance values due to CO_2 , in high age or in the presence of severe reduction of renal function. When the material is classified according to the degree of extrarenal vascular changes present, the same tendency is seen in the group associated with advanced vascular disease, although it is not so marked. Bearing in mind the difficulties of classification and the fact that the correlation between extrarenal and renal vascular changes can hardly be considered to be absolute, this does not seem peculiar.

The general characteristics of the individual cases of hypertension in which there occurred a rise in one or both clearances have been given below in Table 11.

It would seem as though the phenomenon of an inverse response of renal clearances following the administration of CO_2 occurs pre-eminently in females having the red benignant type of hypertension with considerably

Table 11. Characteristics of Cases of Essential Hypertension, exhibiting Increases of one or both Clearances under the Action of CO_2 .

Pat.	Age	Sex.	Eye-grounds	B. P. range	"Nature of hypertension"
I. Increase of both C_{In} and C_{D} .					
E. S.	42	m.	III	230/140—165/115	red, benign
S. S.	49	m.	I	255/140—190/115	" "
A. B.	52	f.	II	275/140—195/130	" "
T. B.	52	f.	III	300/180—220/110	" "
A. H.	57	f.	III	290/140—215/120	" "
B. H.	62	f.	II	220/100—205/115	" arteriosclerotic
H. A.	67	f.	II	255/135—185/100	" "
J. P.	50	f.	I	170/110—130/75	" early or arteriosclerotic
E. P.	52	m.	I	265/120—200/95	normal, arteriosclerotic
E. M.	52	f.	II	285/190—190/100	" benign
J. S.	52	f.	III—IV	295/180—225/140	red, benign
W. B.	54	f.	II	275/125—200/110	" "
M. A.	48	m.	III	220/140—200/120	" "
II. Increase of C_{In} only.					
A. S.	46	f.	I	235/140—190/120	red, benign
A. L.	48	f.	II	260/140—195/100	" "
A. D.	51	f.	0	270/120—170/110	pale, "
K. B.	56	m.	I	220/120—165/95	normal, "
H. J.	53	m.	III	245/130—200/110	red, "
A. P.	49	m.	0	195/105—195/95	" "
III. Increase of C_{D} only.					
H. J.	43	f.	III—IV	275/175—180/105	red, benign

elevated blood pressure values and pronounced retinal changes and in some cases exhibiting arteriosclerotic features.

Sympathectomy and the Influence of Carbon Dioxide on Renal Function.

Owing to facts mentioned in the preface a number of the cases examined pre-operatively could not be subjected to the procedure after sympathectomy as had been planned. The results are given in Table 12.

After sympathectomy a somewhat lower C_{In} and a somewhat higher C_{D} are registered than in the group earlier discussed as established hypertension. After operation the filtration fraction is seen to be within normal limits, which seems worthy of note, as the cases would have been classified as belonging to the groups of established hypertension (4 cases) and hypertension with severe vascular disease (2 cases). The decrease in the average C_{D} under the action of CO_2 appears negligible, although some decreases would seem significant. The increase in average C_{In} would seem definite.

Table 12. Effect of Carbon Dioxide on Renal Function in Essential Hypertension after Sympathectomy.

Pat.	Age	Sex	Date	C _D		C _{In}		F. F.		B. P.		HEMOGLOBIN Per cent of normal standard	RED CELL COUNT	
				Basal	Per cent change	Basal	CO ₂	Basal	CO ₂	Basal	CO ₂			
I. Cases observed before and after sympathectomy.														
S. S. ...	49	f.	11. 7. 46	407	+0.5	94	94	0	0.23	0.23	170/95	190/105	101	5.1 mill.
" ...	"	"	3. 6. 47	337	-15	69	104	+50	0.21	0.27	185/115	220/130	72	4.0 "
			Average	372	+7	82	99	+21	0.22	0.25	178/105	205/118	87	4.5 "
Smithwick I+II, April 1947														
" ...	"	"	6. 5. 47	385	17	81	102	+26	0.21	0.23	170/105	195/115	81	4.2 "
" ...	"	"	10. 30. 47	482	+13	87	110	+26	0.18	0.20	175/115	215/120	89	4.5 "
			Average	434	+15	84	106	+26	0.20	0.22	173/110	205/118	85	4.3 "
E. N. ...	48	m.	10. 28. 46	286	-9	72	80	+11	0.25	0.31	220/120	235/130	102	5.2 "
Smithwick I+II, Nov. Dec. 1946														
" ...	"	"	4. 25. 47	354	-2	63	75	+19	0.18	0.21	180/115	195/115	101	5.1 "
E. S. ...	42	m.	12. 13. 46	304	+9	70	75	+7	0.23	0.23	165/115	180/130	92	4.6 "
" ...	"	"	12. 5. 47	262	+15	49	66	+35	0.19	0.23	210/145	210/150	104	5.2 "
Smithwick I, April+II, Sept. 1947														
Average of preoperative observations				334	+4	76	88	+16	0.23	0.26	185/111	206/124	92	4.7 "
Average of postoperative observations				371	+11	70	88	+26	0.19	0.215	184/120	204/125	94	4.7 "
II. Cases observed only after sympathectomy.														
Peet I+II, Aug. 1945.														
J. H. ...	48	f.	5. 24. 46	542	-	94	-	-	0.18	-	250/150	295/190	-	-
" ...	"	"	10. 12. 47	605	-24	106	110	+4	0.18	0.24	220/115	245/125	-	-
Peet I+II, Nov.-Dec. 1944														
A. B. ...	45	f.	5. 22. 46	597	-14	-	-	-	-	-	195/100	210/115	-	-
Smithwick I+II, March-April 1946.														
H. J. ...	37	f.	5. 1. 46	375	-20	-	-	-	-	-	250/140	285/160	-	-
" ...	"	"	12. 5. 46	424	-8.5	99	94	-5	0.24	0.25	220/115	245/125	-	-
Average of all sympathectomized cases studied with CO ₂														
				435	-6	81	93	+15	0.195	0.23	209/125	236/138	-	-

In the three subjects in which observations were made both pre- and postoperatively the average blood pressure under the influence of CO_2 remained exactly the same and so did the inulin clearance, while there was registered a small rise in diodrast clearance during the CO_2 inhalation (+18 per cent) compared with the preoperative values, which would seem worthy of note in view of the comparatively low level of the initial average C_D (347 cc/min.). Under the action of CO_2 two of the three cases showed increases of 25 and 33 per cent respectively as compared with the preoperative values, while the case with the most advanced vascular disease, E.S., which did not benefit from the operation, exhibited a decrease of 9 per cent.

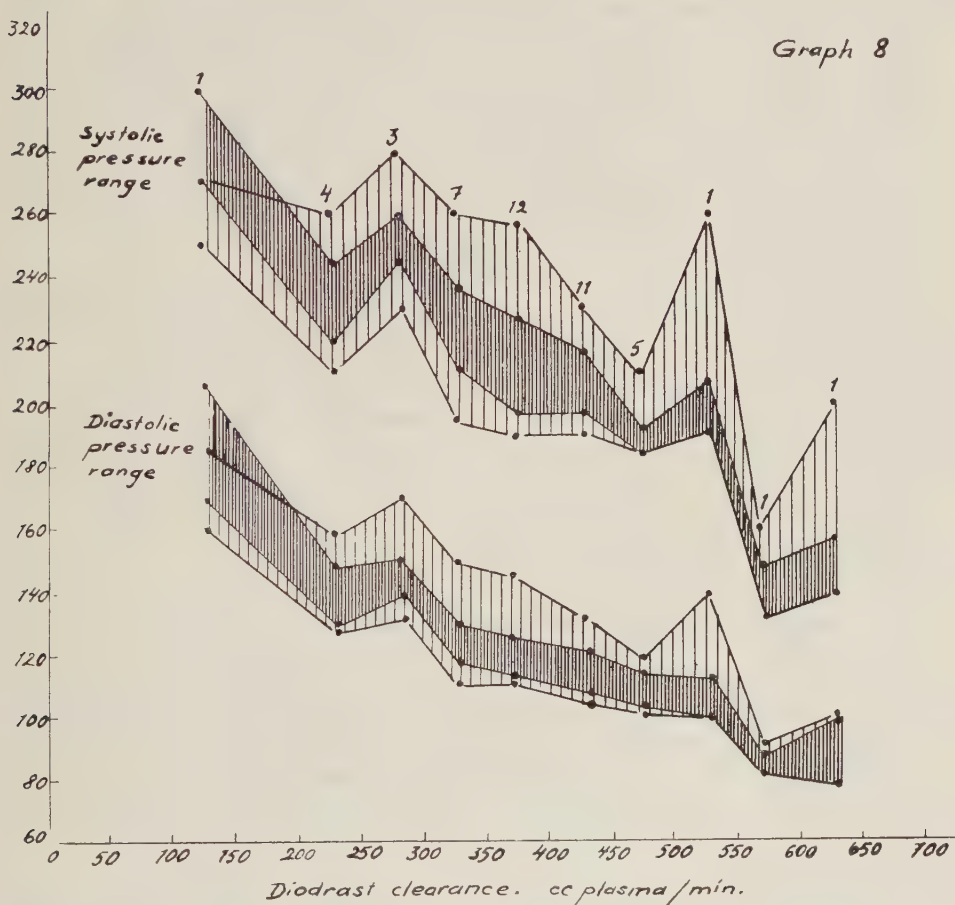
Level and Variability of Blood Pressure and Renal Function.

Assuming that the Goldblatt mechanism exists in man, the level of the C_D should give an idea of to what degree this mechanism is present. For estimating the degree of ischemia of the residual functioning renal tissue, however, the C_D/Tm_D ratio would have been preferable. The influence of various factors on the blood pressure at various levels of C_D is given in Table 13. In this Table two or more observations of the same kind made on the same subject have been averaged and entered as one. The spontaneous variability of the blood pressure refers to the difference between the highest reading, usually taken on patient's admission, and the lowest taken after several days of bed rest. 24 hour readings were not made.

Table 13. Renal Function in Relation to Level and Variability of Blood Pressure.

Range of C_D	Number	Spontaneous Variability of B. P. mm Hg	Fall of B. P. during Hospital Stay mmHg	Number	Fall of B. P. in Amytal test. mm Hg	Number	Difference. B. P. during Renal Study-Lowest B. P. Recorded. mm Hg	Number	Rise of B. P. due to CO_2 mmHg	Number	Rise of B. P. in Cold Pressor Test mmHg
601—650	1	200/100—140/75	60/25	1	25/10	1	+0/0	1	15/20	—	—
551—600	1	160/90—130/80	30/10	—	—	1	+5/0	1	20/5	—	—
501—550	1	260/140—190/100	70/40	—	—	1	+0/0	1	20/10	—	—
451—500	5	211/117—172/104	39/13	3	57/27	4	+2/3	4	18/9	—	—
401—450	11	231/132—189/101	42/31	6	28/13	11	+14/6	11	23/13	6	28/24
351—400	12	255/146—189/114	66/32	6	39/13	11	+12/9	11	32/14	5	15/5
301—350	7	261/149—194/109	67/46	7	57/28	7	+13/5	7	25/14	5	34/16
251—300	3	282/168—227/127	55/41	2	58/20	3	+8/7	3	17/12	1	20/0
201—250	4	260/155—210/125	50/30	2	44/25	4	+11/3	4	24/19	1	40/20
151—200	—	—	—	—	—	—	—	—	—	—	—
101—150	1	270/185—260/160	20/15	1	40/35	1	+20/10	1	30/35	—	—
Average	46		54/31	28	43.5/20	44	+50/5.5	44	22/17	18	26/15

It will be noticed that there is no tendency to a smaller influence of the blood pressure lowering factors, bed rest and the amytal test, or the blood pressure rising, CO_2 and cold pressor test, in cases with severely impaired renal function. However, it is seen that in the low clearance range there is an increased tendency for the blood pressure, especially the diastolic, to remain high after bed rest, although the absolute fall in mm's of mercury from the value found at admission may be very considerable. The drop



The sparsely lined area denotes the range of spontaneous variability of blood while the closely lined area shows the blood pressure rise due to CO_2 . The figures along the line showing the upper limit of the systolic pressures indicate the number of subjects averaged at each respective point. Thus, the significance would seem to be greater in the middle part of the curve. Pressures recorded during the basal clearance studies are seen to be rather close to the lowest reached. With the exception of the subject with the most deteriorated renal function the pressure response to CO_2 is seen to fall rather considerably short of the highest pressures recorded in the same groups of subjects. The significance of these observations will be discussed on page 79.

registered in the amytal test seems rather comparable although smaller than the spontaneous fall due to bed rest. The blood pressures registered during the basal clearance periods seem to be surprisingly close to the lowest. Still, there were a few definite exceptions to this.

The number of cold pressor observations seem too few to warrant any other comment than that the rise in blood pressure appears to be of about the same order of magnitude as that due to CO_2 .

As previously mentioned, the exclusion of cases with advanced cardiac disease because of their unsuitability for CO_2 inhalation should give a series of cases unusually free from pressures influenced by a heart in or on the border to failure. Although the higher average resting blood pressure levels were found in the presence of severely impaired renal circulation, isolated cases with very high pressures and relatively well maintained renal function were also observed, as is to be seen from Table 14. The observations recorded in Table 13 are illustrated in Graph 8.

Summarizing, it may be said that *the present series of cases of essential hypertension is considered to be unusually free from the influence of cardiac factors on the blood pressure levels. In the presence of severely reduced renal function the level of the blood pressure was higher, while the range of variability seemed to be approximately the same throughout the series. Basal clearance studies were performed at an average blood pressure close to the lowest registered. The response to CO_2 during the clearance procedure fell considerably short of reaching the highest pressures recorded for the same subjects.*

Clearance Levels and other Signs of Disturbed Renal Function.

Owing to the necessity of selecting for CO_2 inhalation hypertensive patients with only slight or no signs of cardiac disease, the present series is believed to be unusually free from cardiac factors that might affect blood pressure levels, occurrence and degree of proteinuria and various other states. This seems to justify a short discussion of these points.

In Table 14 two or more clearance determinations on the same subject have been averaged. The cases have been arranged according to falling C_p. The other observations are mostly averages of several determinations, with the exception of the maximal concentration capacity, which in the majority of subjects has been determined only once. Proteinuria was classified on a + to ++++ basis, where + is used to denote slight, inconstant proteinuria, disappearing on bed rest, ++ slight but constant, +++ constantly 1—5 %₁₀₀ protein by the Esbach method, while ++++ would be reserved for cases with more than 5 %₁₀₀. Sediments have only been classified as pathologic or non-pathologic.

Table 14. Clearance Levels and other Aspects of Renal Function in Essential Hypertension. Variability of Blood Pressure.

Pat.	Sex.	CD	C _{in}	Proteinuria	Sediment	Max. conc. capacity	N. P. N.	Eye-gro-unds	Blood pressure
R. A. E. ...	m	610	159	0	0	1.034	—	0	200/100—160/95
G. W.	f	583	106	0	0	1.038	28	—	160/100—130/80
J. J.	m	506	134	0	0	—	40	I	260/140—210/90
S. P.	f	488	—	0	0	1.037	31	I	240/130—185/110
S. S.	m	484	93	0	0	1.030	40	0	200/100—165/100
H. O.	f	465	86	(+)	0	1.021	30	0	180/115—150/90
E. J.	m	461	97	++	+	1.025	37	0	205/130—175/105
T. C.	m	461	84	+	0	—	—	0	230/135—185/115
T. E. A. ...	m	450	100	0	0	1.027	30	0	210/115—130/65
K. B.	m	450	122	0	0	—	—	I	220/120—165/95
E. B.	m	439	153	+	0	1.040	46	I	200/130—175/110
E. A.	f	438	112	0	0	1.024	39	I	260/160—215/120
H. J.	m	435	101	0	0	1.024	42	II	245/130—200/110
O. H.	m	432	—	+	+	1.025	39	II	280/180—170/95
A. P.	m	420	98	0	0	1.022	—	0	195/100—195/95
B. H.	f	417	115	0	0	—	—	II	210/120—205/115
N. Z.	f	417	95	0	0	—	39	I	220/140—140/85
J. O. P. ...	m	411	101	0	0	—	—	I	170/110—130/75
S. L.	f	407	112	+	0	1.015	40	III	290/190—250/140
A. D.	f	397	85	0	0	1.022	30	0	270/120—170/110
L. W.	m	386	103	0	0	1.025	46	I	235/145—180/110
T. S.	f	380	107	0	0	1.023	33	II	320/220—240/135
H. A.	f	376	94	0	0	—	—	II	255/135—185/100
S. N.	f	376	72	0	0	—	35	—	250/140—210/120
S. S.	f	372	82	0	0	—	35	I	235/140—190/115
K. W.	f	367	96	+	0	1.029	34	II	310/170—190/110
E. P.	f	367	80	0	0	1.025	39	I	265/120—200/95
A. L.	f	366	96	0	0	1.032	26	II	260/140—195/100
H. P.	f	356	92	+	0	1.023	31	—	210/110—160/115
B. G. B. ...	m	355	86	++	0	1.016	31	IV	280/180—200/150
M. A. O. ...	f	354	81	+	+	1.030	38	III	260/140—220/140
M. L.	f	352	—	0	0	1.024	34	I	195/120—140/85
E. M.	f	347	92	0	0	—	36	II	285/190—190/100
A. S.	f	346	76	+	+	1.027	34	I	235/140—190/120
H. J.	f	340	92	++	+	1.019	32	IV	275/175—180/105
G. J.	f	310	58	0	0	1.020	31	II	235/140—220/110
A. M. H. ...	f	308	65	0	0	1.026	21	II	290/140—215/120
E. S.	m	304	70	++	+	1.015	41	III	240/140—165/115
E. N.	m	286	72	0	0	1.018	35	II	250/140—215/105
E. A.	f	256	80	++	+	1.027	40	IV	320/240—265/165
W. B.	m	255	77	+	+	1.024	33	III	275/125—200/110
T. B.	f	250	63	++	+	1.023	26	III	260/140—220/110
J. S.	f	246	66	+++	+	1.021	35	IV	295/180—225/140
A. B.	f	242	55	++	+	1.021	40	II	265/160—195/130
M. A.	f	241	63	+	+	—	24	III	220/140—200/120
K. J.	m	137	37	+++	+	1.008	45	IV	270/185—250/160
Sympathectomized subjects.									
J. H.	f	574	106	0	0	1.028	39	I	270/135—220/115
A. B.	f	597	—	0	0	1.024	—	—	240/110—160/110
S. S.	f	434	84	0	0	—	—	I	220/125—170/105
H. J.	f	400	99	+	+	1.024	39	IV	320/190—220/115
E. N.	m	354	63	0	0	—	—	II	190/115—130/80
E. S.	m	262	49	++	+	—	—	III	220/150—190/130

Proteinuria, persisting during bed rest, is seen from Table 14 to occur almost exclusively in the low clearance range. The exception to this, E.J., was a 34 years old male who for many years had suffered from: nephrolithiasis and who had undergone a left pyelolithotomy between his two admissions for clearance studies. The observation that constant proteinuria occurs only in the presence of advanced derangement of renal function seems to correspond with clinical experience. Goldring and Chasis (1944) found constant or pronounced proteinuria only when the Tm_D level was at or below 20 mg/min. *Thus, one may venture to state with a high degree of certainty that constant proteinuria in an ascertained case of essential hypertension denotes a severe reduction of renal function (by about 50 per cent or more) if manifest or impending cardiac failure can be excluded.* With the exception of a few cases having extremely elevated blood pressures, no loss of maximal concentration capacity was seen to occur until approximately the same low clearance levels were reached. Throughout the series there was no rise in the nonprotein nitrogen values.

The increased frequency and severity of retinal lesions occurring in advanced impairment of renal function is also clearly seen.

CHAPTER V.

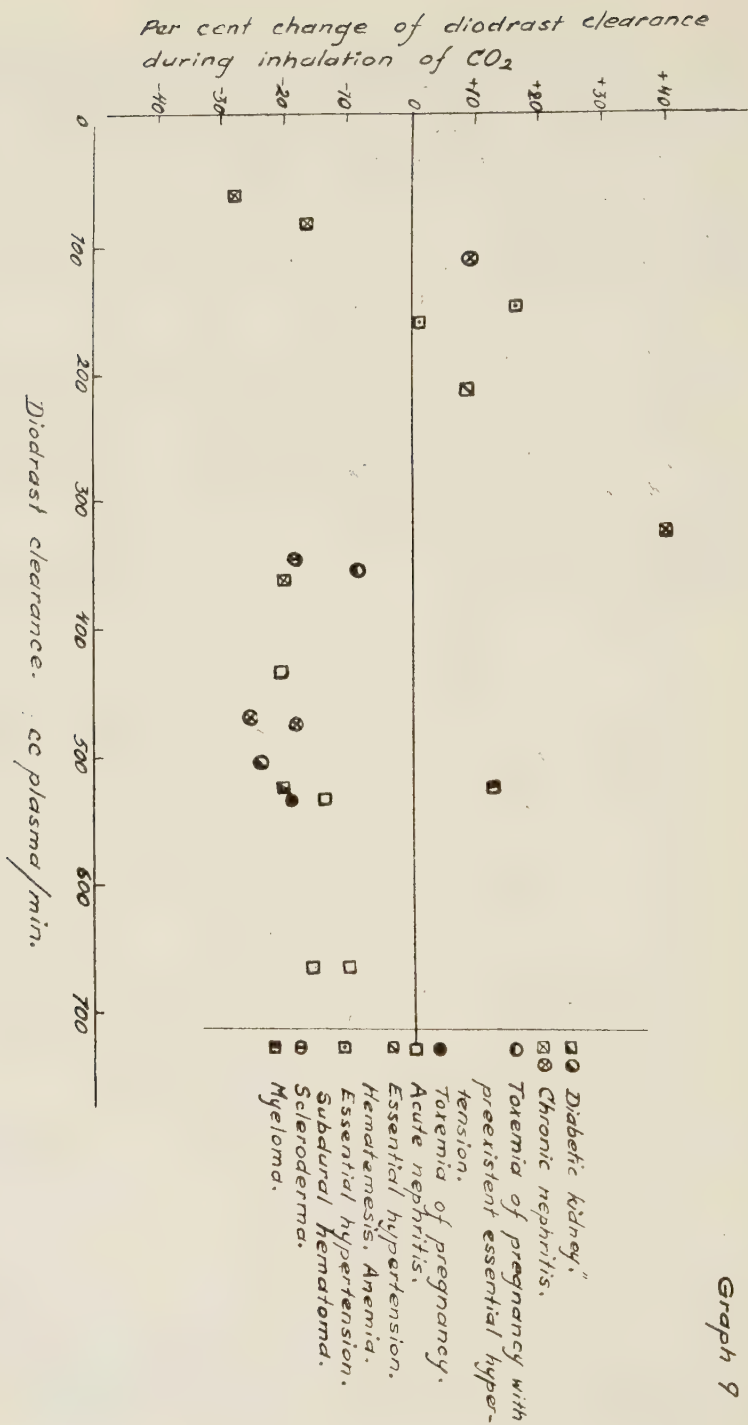
Effect of Carbon Dioxide on Renal Function in Various Kidney Disorders.

Although the writer's attention was primarily focused on essential hypertension, there arose during the course of the investigation a certain demand for detailed kidney studies in a number of miscellaneous kidney disorders. As the results are thought to have some bearing on the interpretation of the changes in renal clearances in hypertension due to CO₂, they will be discussed at some length.

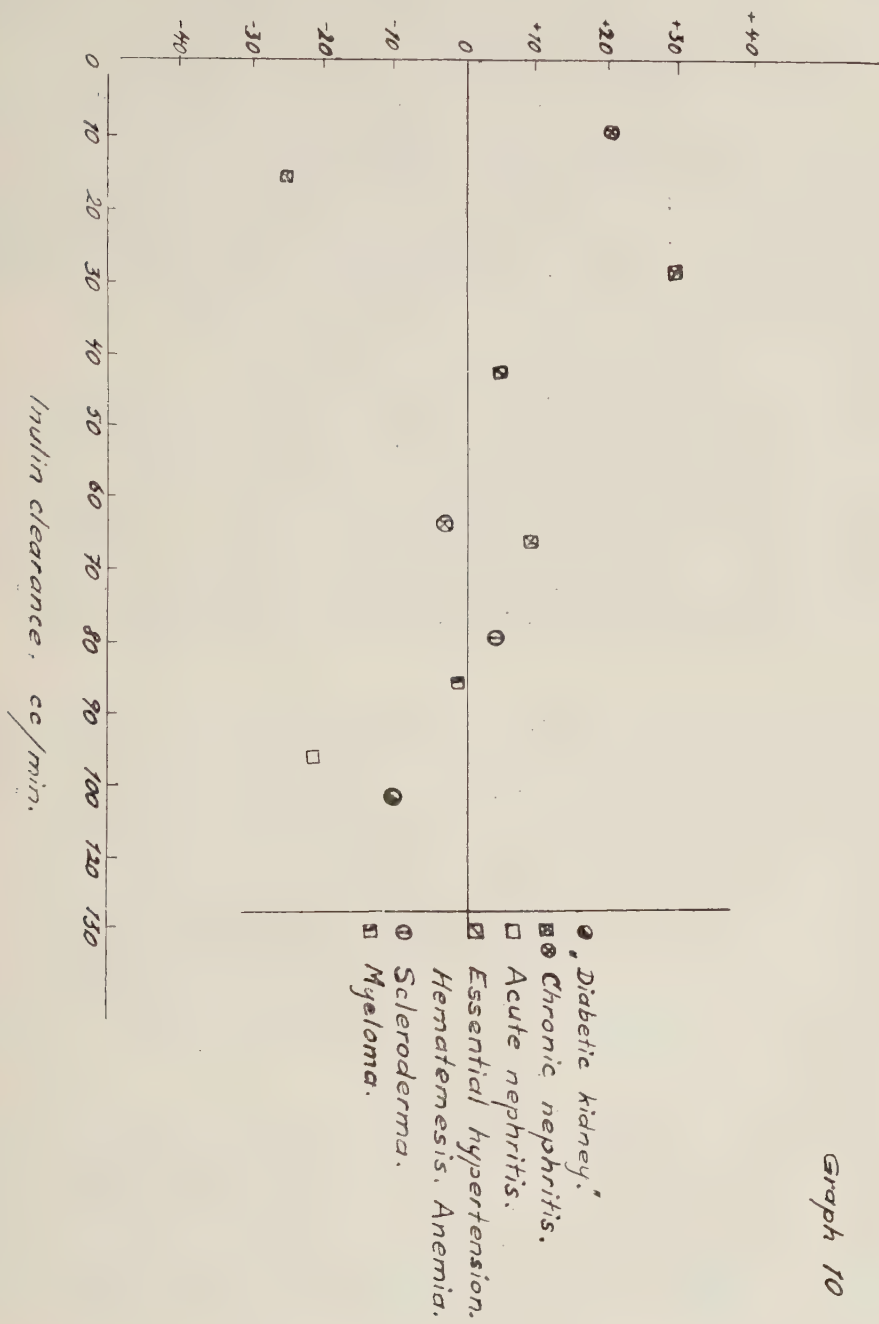
Table 15. The Effect of CO₂ in Renal Clearances in Various Kidney Disorders.

Pat.	Age	Sex	C _D			C _{In}			FF	
			Basal	CO ₂	Per cent change	Basal	CO ₂	Per cent change	Basal	CO ₂
Acute and subacute glomerulonephritis										
E. L.	26	m	662	595	-10	—	—	—	—	—
B. H.	27	m	668	567	-15	97	76	-22	0.13	0.14
»	27	m	528	457	-14	—	—	—	—	—
J. K.	21	m	438	344	-21	—	—	—	—	—
Chronic glomerulonephritis.										
E. J.	38	f	470	348	-26	64	62	-3	0.13	0.18
A. S.	67	f	472	384	-19	—	—	—	—	—
A. E.	45	m	368	295	-20	67	73	+9	0.18	0.25
P. A. J. ...	50	m	320	426	+33	29	37	+28	0.09	0.09
M. A.	55	f	117	127	+9	10	12	+20	0.08	0.08
E. L.	44	m	85	71	-17	—	—	—	—	—
A. L.	42	m	68	49	-28	16	12	-25	0.23	0.24
Diabetic kidney.										
K. A.	23	f	500	380	-24	102	92	-10	0.20	0.24
L. B.	20	m	521	415	-20	—	—	—	—	—
Toxemia of pregnancy.										
A. J.	41	f	525	440	-19	—	—	—	—	—
Toxemia of pregnancy with preexistent essential hypertension.										
E. J.	37	f	358	327	-8	—	—	—	—	—
Essential Hypertension. Hematemesis. Anemia.										
A. L. B. ...	54	m	217	234	+8	43	45	+5	0.20	0.19
Essential Hypertension. Subdural Hematoma.										
F. O. J. ...	47	m	164	167	+2	42	42	0	0.26	0.25
»	47	m	148	172	+16	33	38	+15	0.22	0.22
Multiple Myeloma.										
A. J.	46	m	520	590	+13	86	85	-1	0.16	0.14
Scleroderma.										
H. B.	49	f	346	281	-19	80	83	+4	0.23	0.30

In Table 15 use has been made of the non-committing term diabetic kidney. Both patients showed slightly elevated blood pressure values, diabetic retinitis and moderate proteinuria, the latter in one of the cases



Per cent change of inulin clearance
during inhalation of CO_2



being inconstant. There was no tendency to edema. Two cases of essential hypertension in which there was a co-existent condition that could probably influence the renal function have been included in this series, it being regarded as preferable to treat them here instead of in connection with the series of essential hypertension.

It may be of some interest that the two subjects with chronic nephritis and with exceptionally low filtration fractions both showed distinctly raised blood pressures at the time of the renal study.

Followed up for 2 1/2 years, both proved to be in better shape at the end of this period than at the time of renal study. This seems to be in accord with the suggestion made by Hogeman (1948) as to the comparatively good prognosis of cases with chronic nephritis presenting low filtration fractions even if the filtration rate is greatly reduced.

The case of scleroderma did not present hypertension or renal disease in its history or in the routine clinical work-up. The clearance test was technically satisfactory and showed a rather good check between the four control periods. The diodrast clearance was definitely lower than any found in the present control series. As this was a case with rather advanced esophageal lesions, and as there are reports of other visceral manifestations in this disease (for a review reference is made to Allen, Barker and Hines, 1946), the observation has seemed worthy of note.

A visual impression of the changes due to CO_2 is gained in Graphs 9 and 10.

Except in the case of myeloma, it is seen that regardless of the pathologic condition underlying the reduced renal function there is a fall in C_D due to CO_2 in the presence of slightly or moderately impaired function. This fall corresponds approximately to the reduction in C_D registered in essential hypertension at the same clearance levels. At about a C_D of 300 cc/min. there is noted a tendency for inverted responses to occur. The five observations in this range showing increases of C_D include 3 observations in cases with rather severe essential hypertension complicated by a condition that could not be definitely stated not to exert an effect on renal function, and 2 observations in cases of chronic glomerulonephritis with considerable and longstanding hypertension.

The two cases with extreme reduction of C_D show a fall under the action of CO_2 . This corresponds with the observations made in the case of malignant hypertension with the most severely reduced function in the series of essential hypertension and in two cases of chronic glomerulonephritis with extremely reduced C_D examined by the single intravenous injection technique. Thus, in the five cases with the most advanced renal functional impairment there has occurred no rise in C_D due to CO_2 .

Whether the fall observed is significant or not, is difficult to tell. In absolute terms it is small. *These observations seem, however, to argue against the possibility that the increases due to CO_2 usually observed within the C_D range 150—350 cc/min. might be explained by some peculiar phenomena of diodrast excretion occurring in the more severely damaged kidneys under the action of CO_2 .*

The observations on C_{In} are rather few. Below a clearance of about 80 cc/min, the same tendency is noted to an unchanged level or increase in C_{In} due to CO_2 as in the cases of essential hypertension. In absolute terms the 25 per cent reduction found in the case with C_{In} of 16 cc/min means only a change of 4 cc, which, of course, is of doubtful significance.

CHAPTER VI.

Observations on the Effect of Carbon Dioxide in Experiments with the Single Intravenous Injection Technique.

As previously mentioned, this technique was abandoned because of the successive drop of clearance values that was encountered in practically every case. Only in a small number of cases was the CO_2 inhalation interposed between basal periods. The observations in essential hypertension have been summarized in Table 16, though they are considered to be of very limited value.

Table 16. Effect of CO_2 Inhalation on Cd in Essential Hypertension at Different Clearance Levels (Single Intravenous Injection Technique).

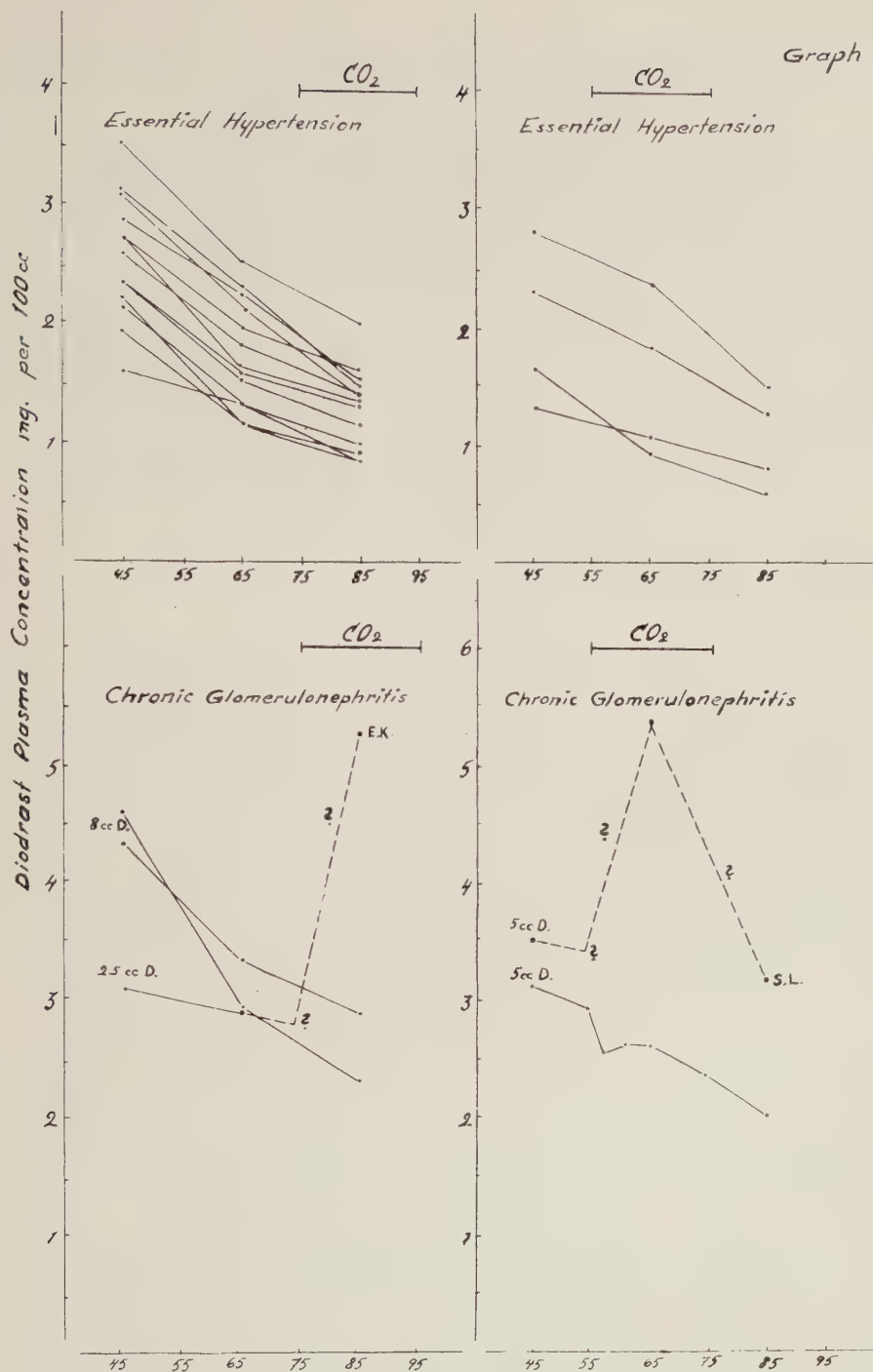
Clearance level. cc/min.	Number of cases	Average Cd		Per cent change during CO_2
		Basal	CO_2	
401—450	4	419	262	—37
351—400	3	389	287	—26
301—350	9	330	261	—20
251—300	2	263	295	+12

There is seen to be an inverted response at the level between 250 and 300 cc. The drops at the other levels appear larger than the corresponding figures in the series examined with the continuous infusion technique. This would seem to be naturally explained by a summation of the effect of the spontaneous drop and the effect of CO_2 .

Plasma concentrations showed the drop registered by a number of authors. Surprisingly enough, however, in two cases of terminal chronic glomerulonephritis with extreme reduction of renal function and considerable azotemia there was a definite elevation of the plasma diodrast concentration during the CO_2 inhalation period. In one of these cases there was sufficient plasma left to make a third determination in addition to the usual duplicate analyses. This phenomenon is illustrated in Graph 11.

Data on the two cases of terminal azotemic chronic glomerulonephritis, including the calculated clearances of diodrast, which naturally are thought to diverge grossly from the actual renal plasma flows, are submitted in

Graph 11



Minutes after single intravenous injection of 10 cc. Diodrast

Table 17. The Rehberg creatinine tests were performed a few days before the diodrast tests.

Table 17. Effect of CO_2 on plasma diodrast concentration in terminal azotemic chronic glomerulonephritis after a single intravenous injection of diodrast.

Pat.	Age	Sex	CCr cc/m.	N. P. N. mg/100 cc	Diodrast study					
					Urine flow cc/m.	U I mg/100 cc	UV mg I	P _D	UV/P	
S. L.	49	f	24	80	1.56	128	2.01	3.50	58	CO_2
					1.59	62	1.07	5.35*)	20	
					1.60	61	1.07	3.16	32	
E. K.	54	m	4	100	2.0	46	0.92	3.08	30	CO_2
					1.6	29	0.47	2.88	21	
					0.78	39	0.31	5.24**)	6	

*) Triplicate analyses 5.26, 5.31, 5.42.
 **) Duplicate analyses 5.12, 5.36.

In Table 17 P_D is seen to be very considerably higher under the action of CO_2 than during control periods without a corresponding increase in the urinary diodrast output. Assuming these two observations to be accurate, there seem to exist some alternatives by which to explain why no increase in urine diodrast was observed. For instance, the tubular saturation limit could be so closely approached or even reached in these severely damaged kidneys that no further rise in tubular excretion could occur, the increase in filtered diodrast at these low filtration rates being insufficient to give a clearly significant increase in urinary diodrast. A second possibility might be that in these cases CO_2 could exert a depressive influence on the tubular diodrast excretion. However, the increase in the total diodrast content of the circulating plasma seems to be so large that, at a normal rate of diodrast transfer from the tissues into the plasma, even a complete suppression of the renal excretion would have been entirely insufficient to explain the rise in plasma diodrast. The third possibility would seem to be that under the action of CO_2 diodrast is mobilized and transferred to the plasma from a deposit somewhere in the tissues. Olivet (1931) found no evidence of deposition of "Abrodil" in either normal dogs or in one with a "contracted kidney" and severe azotemia. With "Perabrodil" (diodrast) Lengeman (1933) found a deposition in the skin and the liver, which was considerably increased in nephrectomized animals. Brun, Hilden and Raaschou (1948) found the venous plasma diodrast concentration to lie higher than the arterial, when a falling curve was used, and thought this

to be due to the skin and other dépôts yielding up diodrast when the diodrast plasma concentration was falling. This was considered to be the reason for the considerably lower values for C_p found when the single intravenous injection technique is used. To the writer the most probable explanation of the increase in plasma diodrast in the two cases discussed above seems to be a mobilization of diodrast from a deposit in the skin. Stasis during the collection of the blood sample might further increase the values.

In the series examined with the continuous intravenous injection technique, only in the case of chronic glomerulonephritis with the most extreme reduction of renal function was a slightly similar observation made, the plasma concentrations being 2.80, 3.24 (CO_2) and 2.96. Thus, it should be possible to rule out this particular source of error in the cases examined with the continuous infusion technique.

CHAPTER VII.

Effect of Carbon Dioxide on Urine Flow.

Owing to slight differences in the forcing of fluids in different subjects in the attempts to keep a high diuresis the experimental conditions for studying the effect of CO_2 were not good, as the administration of CO_2 could happen to coincide with the very peak of the water diuresis just as well as with the latter's ascending or descending limb. In the dog, Springorum and Centerea (1937) showed a considerable reduction of diuresis even under conditions of urea diuresis. In the present material cases classified as belonging to the same groups of patients could show very large differences in both directions. The inulin U/P concentration ratios appeared to show the natural inverse relation to the diuresis with no or negligible demonstrable influence from CO_2 . Thus, no decisive influence of CO_2 on the urine flow comparable with that exerted by the forcing of fluid could be observed. Table 18 gives the average changes in diuresis due to CO_2 in the various groups of cases.

Table 18. Effect of CO_2 on Urine Flow.

	Number of subjects	Urine flow cc/min.		Per cent change
		Basal	CO_2	
Normals	25	5.1	4.1	-20
Essential Hypertension				
Early hypertension	15	7.11	7.59	+7
Established hypertension	32	5.24	6.42	+22
Established hypertension with severe vascular disease	15	5.43	6.66	+23
Malignant hypertension	5	2.89	3.52	+21
Arteriosclerotic hypertension	3	3.5	3.5	+0
Hypertension; all cases Average	70	5.45	6.25	+15
Essential Hypertension Sympathectomized	10	5.42	7.26	+34
Acute Glomerulonephritis.....	6	5.59	7.79	+41
Chronic Glomerulonephritis.....	10	5.5	4.73	-14
Miscellaneous Kidney Cases.....	11	4.46	5.22	+17

The decrease of the averaged urine flow in the normals is seen to be in some contrast to the observations in the other groups, with the exception of the small group of cases with chronic glomerulonephritis. In view of the very large differences between individual subjects it seems uncertain whether much significance should be attached to this difference between normals and the kidney cases in general.

The Effect of Carbon Dioxide on Blood Pressure.

Irrespective of the clearance technique used, all cases are submitted in Table 19.

Table 19. Effect of CO₂ on Blood Pressure

Combined series. (Continuous intravenous infusion studies and single intravenous injection.)

	Number of subjects	Basal		CO ₂		Change	
		B. P. Syst.	mmHg Diast.	B. P. Syst.	mmHg Diast.	Syst.	Diast.
Normals	25	124	77	141	89	+17	+12
Essential Hypertension							
Early hypertension	15	152	93	175	106	+23	+13
Established hypertension	32	196	112	222	129	+26	+17
Established hypertension with severe vascular disease	15	238	139	260	156	+22	+17
Malignant hypertension	5	240	153	271	178	+31	+25
Average	67	200	117	222	135	+22	+18
Arteriosclerotic hypertension	3	197	105	217	114	+20	+9
Hypertension; all Cases Average	70	200	116	222	133	+22	+17
Essential Hypertension Sympatectomized	10	203	120	234	136	+31	+16
Acute Glomerulonephritis	6	138	86	153	99	+15	+13
Chronic Glomerulonephritis	10	158	93	177	109	+19	+16
Miscellaneous Kidney Cases	11	144	94	161	103	+17	+9

It seems of some interest that the group of sympathectomized cases showed an average pressure increase closely comparable to the mean for the entire unoperated-upon series. The pressure increase in the small group of cases classified as malignant seems to show a higher response than any other group.

Using CO₂ mixtures of 3.5—5.4 per cent and a system with a free outflow Raab found the following pressure response.

	Systolic	diastolic
Normals	+ 12	+ 8
Essential H.	+ 21	+ 12.

With a rebreathing system Raab encountered untoward reactions after 7—10 minutes, but stated the systolic blood pressure rise to be approximately thrice as pronounced in cases of essential hypertension as in normals. There appears to be a possibility that the lower response in the present series could be due to the longer time of observation, the impression being that the values tended to drop slightly during the CO₂ inhalation.

The comparison with these results of Raab and the experience gained during the work have given the impression that the type of CO₂ administration used is about the heaviest dosage that could reasonably be given to this type of cases for the length of time used in this study (12—30 minutes).

CHAPTER VIII.

Discussion of Results.*Significance of the Changes in Clearances occurring under the Influence of CO₂.*

As there occurs a uniform rise of blood pressure the depression of C_D registered during inhalation of CO₂ in all cases with normal, slightly or moderately reduced renal function might theoretically be explained by any of the following possibilities.

1. A vasoconstrictor action leading to either
 - a. a more or less uniform decrease of plasma flow throughout the kidney, or
 - b. a shunting of the blood from excretory cortical to non-excretory medullary tissue.
2. A decrease in the ability of the tubular excretory mechanism to secrete diodrast, even at the low plasma levels used for the determination of C_D .
3. An alteration of the red cell/plasma shift of diodrast under the influence of CO₂.

Direct evidence of the behaviour of the extraction ratio under the action of CO₂ has not been obtainable, as the local conditions have not permitted renal vein catheterization. The following reasons are however thought to argue in favour of a vascular and against a tubular site of action of CO₂. The profound changes of renal hemodynamics found in hemorrhagic shock in dogs (Van Slyke, 1948) and under the application of abdominal pressure in man (Bradley and Bradley, 1947), had no effect on the extraction ratio. Considerable depressions of T_{mp} by mersalyl in therapeutic doses without affecting the C_D measured at low plasma levels (< 1 mg per 100 cc) were found by Brun, Hilden and Raaschou (1947).

In the dog, the direct thermostromuhr measurements of the Rein school showed larger decreases of renal blood flow than those registered in the present series.

By direct observation (Adolph, 1935) the glomerular blood flow was seen to become sluggish or to stop entirely in the frog under the influence of high tensions of CO₂ (30—70 per cent by volume). The urine flow was severely or completely inhibited, but as a rule it rose very quickly to control values after change to normal atmosphere. In the present writer's experience, clearance periods immediately following the end of the CO₂ inhalation often showed figures closely approximating those of the preceding control periods.

The observations of an abolished or inverted response to CO_2 with an unchanged or raised C_D in cases with severely reduced renal function in the present series seem to speak strongly against the possibility of a decreased extraction ratio.

Thus, it is considered that the fall of C_D under the action of CO_2 is exclusively due, or almost so, to the vasoconstrictor properties of this agent. The simultaneous tendency to a fall in C_m , although not quite so large, would seem to point to a participation of the afferent arterioles.

The tendency to unchanged or raised clearances produced by CO_2 in the presence of severely reduced renal function or after the age of 45—50 in the series of essential hypertension seems to the writer to offer no other probable explanation than the presence of advanced renal arteriosclerosis. This could easily be conceived to make the renal arteriolar walls less subject to the neurogenic vasoconstrictor effect of CO_2 , the increased blood pressure being brought to bear more directly on the glomeruli, increasing filtration pressure and the rate of filtration. As in most cases the increase of filtered diodrast would be insufficient to explain the rise in C_D , it seems as if there may occur a simultaneous increase in effective renal plasma flow.

The demonstration of normal efferent arterioles even in the presence of advanced afferent arteriolar sclerosis (Mc Gregor, 1930) might make the reactions of the two sets of arterioles somewhat different. *It would be quite possible for CO_2 or any vasoconstrictor agent to exert a decreasing influence, preferably on the afferent arteriole, as the arteriosclerotic process advanced in the kidney, at the same time maintaining its effect to a larger extent on the less affected efferent arteriole. This would favour the establishing of the high filtration fractions actually found.*

The kidney in terminal chronic Bright's disease shows an extensive rebuilding of the normal architecture (Oliver, 1942). The possibility of peculiar and unpredictable phenomena of diodrast excretion occurring under the action of CO_2 cannot be entirely rejected, such as for instance mobilization of focally stagnating, diodrast-containing tissue fluid. This alternative is however considered as very remote, since — including the two determinations performed with the single intravenous injection — the five cases with the most severely reduced renal function showed a decreased output during the CO_2 inhalation. These were four cases of terminal chronic glomerulonephritis and one of extremely malignant hypertension.

Selkurt (1946) held that the pressure-flow relationships of the kidney could be explained by a change of the physical factors affecting the blood stream. According to this author, the apparent constancy of renal blood flow at varied blood pressure levels (Landergren and Tigerstedt; Rein;

Unna as well as Morimoto) should not be ascribed to an intrinsic autonomic activity of the vessels of the kidney.

In the present series the increased filtration under the action of CO_2 in cases with severely reduced function should tend to increase the blood viscosity and hence the resistance to blood flow. From this point of view the observed increases in C_D would gain in weight.

The possibility of an intramedullary redistribution of blood such as that shown by Trueta and coworkers for the rabbit's kidney being responsible for the fall of C_D in the kidney with normal to moderately reduced renal function seems less probable for the following reasons.

The direct measurements in the dog (Rein *et al.*) produced what seem to be larger decreases in renal blood flow than the present indirect measurements in man.

Trueta and his coworkers were impressed by the frequency of juxtamedullary glomeruli of degenerate type in cases of essential hypertension, and suggested that a permanent diversion of cortical blood flow could be created by these changes. They thought that at such a stage much of the increased circulation due to a rise of blood pressure would be drained away through the medullary pathway before it reached the cortex.

In the present study there was a tendency to an increase in filtration and effective renal plasma flow by the action of CO_2 , presumably due to the B.P. rise, in cases of essential hypertension and chronic nephritis with renal function reduced 50 per cent or more. These are just the type of cases in which the anatomical possibilities for a "Trueta mechanism" should be good. Quite naturally, these observations cannot be taken as a definite proof that a mechanism of this nature is not operative in these cases, as the observed increases in clearances could be explained by the net outcome of a considerably increased filtration and blood flow in some cortical areas, with a simultaneous medullary diversion of part of the blood. In the juxtamedullary vascular pathways described, with their degenerate or vanished glomeruli, filtration or excretion would certainly be small or non-existent.

The results are however thought to throw some doubt on the quantitative functional significance of the anatomical observations of Trueta and co-workers in essential hypertension. As the rabbit's circulation differs much from man's, and as means for experimental approach to the problems of the intrarenal distribution of blood in the human kidney seem to be available, it would probably be wise to suspend judgment as to whether a "Trueta mechanism" of quantitatively significant importance occurs in the anatomically intact or diseased human kidney. The brilliant work of Trueta and his group should certainly serve as a challenge.

The alterations of the ionic interchange that have been shown to occur between red cells and plasma when CO_2 is added to blood (Hamburger) might seem to open up the question of a changed red cell/plasma shift of diodrast during renal passage. Direct evidence on this problem seems difficult to acquire. However, considering the extremely rapid removal of plasma diodrast that must occur during renal passage, it would seem improbable that at the same time significant amounts of diodrast should penetrate into the red cells. If the shift that is thought to occur in the other direction should increase under the action of CO_2 , it would result in more diodrast being offered to the tubular cells for excretion, and hence the apparent renal plasma flow would be increased. This would tend to counterbalance the observed falls. Furthermore, the entirely opposite changes of C_D registered at the different levels of renal function as well as the simultaneous and analogous alterations in C_{In} seem to argue against this source of error playing a role that could invalidate the conclusions.

The comparatively scanty evidence as yet available on the tubular mode of diodrast excretion in the severely diseased kidney appears to point towards a handling of diodrast in the normal fashion by the remaining functional tissue (Smith; Earle, Taggart and Shannon; Josephson; Raaschou). Judging from the series of cases reported by Goldring and Chasis (1944), the cases of essential hypertension in the present study, with the possible exception of the case of malignant hypertension with the most severely reduced renal function, would probably be in the range of a T_{mp} above 15—20 mg/min. Thus, they would be over the levels at which Earle, Taggart and Shannon observed a falling off of the values of T_D in relation to the tubular diodrast load in chronic glomerulonephritis. The possibility must be taken into account that the increased blood pressure due to CO_2 might raise the blood flow proportionally more to the regions with the most advanced arteriolosclerotic changes, where the amount of inert scar tissue, inactive nephrons and possibly "impotent" tubules should be highest. As a consequence, the observed increases of C_D might not be quite so large as the actual rises in renal blood flow that may have occurred.

Sympathectomy and Renal Function.

The absence after sympathectomy of consistent C_D increases of clearly significant magnitude, comparable with for instance those induced by the pyrogenic reaction, has been taken as an argument against neurogenic and for humoral origin of the ischemic tendency of the kidney in essential hypertension (Smith, 1943; Goldring and Chasis, 1944). However, the problem whether there exists a tonic or intermittent neurogenic activity in

essential hypertension that influences the renal circulation seems to the author to be highly complicated.

Three possible sets of factors might be conceived to participate in varying degree in the production of renal ischemia in essential hypertension, *viz* (1) organic vascular changes, (2) humoral pressor factors and (3) neurogenic vasoconstriction. From the literature the impression is gained that those sympathectomized cases in which renal function has been studied have presented rather advanced vascular changes as evidenced by renal biopsy grades (mostly 3, Talbott *et al.*), fundusoscopic findings (mostly Keith 3, 2 and 4, Foa *et al.*). The same impression is received from the majority of the clearance values reported when these are compared with the present series. That the organic vascular changes lead to a considerable decrease of renal function seems rather clear from the studies of Oliver (1942), who claimed that in every one of his cases all the changes in the senile kidney could be accounted for by organic vascular origin. The pronounced general decrease of renal function with increasing age has already been discussed. Bell's extensive studies (1947) showed the vascular changes to be more pronounced in younger hypertensive than in older non-hypertensive groups. The present writer firmly believes that organic vascular alterations had a considerable share in the reduction of renal function among most of the sympathectomized cases reported in the literature,

Despite the failures to prove the existence of circulating vasoconstrictors in chronic essential and malignant hypertension (reviewed by Braun-Menendez *et al.*, 1946) there still seems reason to assume that a production of pressor factors capable of exerting an influence on the renal circulation might occur in at least the cases with comparatively severe impairment of renal function due to any cause whatever. Still, it appears unwise to exclude the possibility of neurogenic factors participating.

There is a difficulty in judging whether renal denervation has been complete in sympathectomy. Moreover, after a successful sympathectomy it seems very difficult to evaluate the influence of the blood pressure fall on the renal function in cases with varying degrees of renal arteriolar changes.

In studies conducted under high spinal anesthesia Gregory, Levin, Ross and Bennet found, in cases of essential hypertension, very considerable decreases in the clearances of inulin and diodrast, roughly proportional to the amount and duration of the fall in blood pressure and rising with the blood pressure to normal values during the second experimental hour. In one patient there occurred an inexplicable rise of blood pressure and a simultaneous increase in clearances. Similar results have been reported

earlier by Berglund, Medes, Benson and Blumstein, (1935), who used the creatinine method.

To exclude with certainty the existence of neurogenic factors of a tonic nature on the kidney circulation of the resting, recumbent case of essential hypertension, it would appear necessary both to have a reliable method of ascertaining whether renal denervation was complete and to provide, if possible, approximately the same pressure head in the renal artery as before operation. This is thought to be desirable, as the pressure-flow relationships of a kidney with rather considerable arterio- and arteriolo-sclerotic changes might easily be capricious.

As was pointed out by Smith and his associates, every attempt to exclude extraneous and emotional stimuli is usually made during the clearance procedure. In the present series the generally high degree of success of these measures seems to be illustrated by the fact that the averaged blood-pressure levels at the renal functional study are only slightly higher than the lowest pressures recorded and very much lower than the highest reached in the same patients.

The probably rather safe assumption is made that the zone between the highest and lowest pressure found in this study really represents approximately that within which the blood pressure of the hypertensive individual usually oscillates during day and night in his active life. Hence the point might be raised as to what extent the renal hemodynamic pattern when measured at the higher levels may differ from the one registered at a pressure usually very close to the lowest reached after several days of bed-rest.

The question arises of the extent to which the increase in blood pressure due to CO_2 in the various vascular regions involves changes that might be representative of the effect of the varied neurogenic stimuli that might occur. In the resting condition Prinzmetal and Wilson (1935) and Pickering (1935) found that the blood flow through the limbs in hypertensive subjects closely approximated the rate registered in normal controls under normal conditions, as well as under novocaine block and heating of the body. This was taken to indicate that the splanchnic area was not constricted more than the vessels of the extremities.

CO_2 has been shown to produce a decrease in the blood flow of the leg of normal man (Lennox and Gibbs), of the intestinal vessels in the rat (Dale and Evans), of the kidney, in the frog (Adolph), in the dog (Rein and associates; Springorum) and in man (present study). On the other hand, a considerable increase has been shown in the cerebral blood flow under the action of CO_2 (in man, Lennox and Gibbs; Kety and Schmidt). As is seen, it would have been unsafe to conclude from the observation of a

decreased blood flow through the leg that this had any bearing on the state in other vascular regions.

In normals decrease in renal blood flow has been demonstrated to occur under the influence of fright and apprehension (Smith), standing posture (Brun, Knudsen and Raaschou), pain (Wolff, George A.) and after strenuous exercise (Barclay, Cook, Kenny and Nutt).

There can hardly be reason to assume that this variety of external stimuli would not be operative in hypertensive subjects.

In fact, "traumatic interview" has recently been shown to produce consistent moderate depressions in renal plasma flow (Wolff, Pfeiffer, Ripley, Winter and Wolff, 1948).

Theoretically, the blood pressure rise brought about by the multitude of external stimuli could exert a renal vasoconstrictor effect less than (possibly none at all) or more than or equal to a comparable rise induced by CO_2 . If the renal influence should be equal to or stronger than that exerted by CO_2 , renal hemodynamics could readily be conceived to differ very considerably from the bed-rest pattern, as the average pressure increase due to CO_2 falls considerably short of the highest pressures recorded during spontaneous variability.

On the other hand, if the temporary rises of blood pressure are assumed to exert less renal arteriolar influence than CO_2 , or a negligible one, the renal hemodynamic conditions at higher blood pressure levels might very well be the same as during bed rest in hypertensive subjects with slightly or moderately reduced renal function. If the writer's interpretation of the inverted responses in cases with severely reduced renal function is correct, a blood pressure rise not due to CO_2 in these cases with a small or negligible renal arteriolar influence would probably tend to exaggerate the increases in filtration and renal blood flow.

Since the decreases of renal blood flow registered under the action of apprehension, strenuous exercise, standing posture and carbon dioxide are seemingly of about the same order and rather similar to the effect of 1 mg of adrenalin, there would seem to be some probability that the various identifiable and non-identifiable stimuli of active life would affect the renal circulation in approximately the same way.

Anyhow, it seems hardly justifiable to draw conclusions of the possible rôle of the renal nerves in essential hypertension from experiments performed before and after sympathectomy, where the examination is made after several days of bed-rest, and care has been taken to cut down the influence of extraneous stimuli. Significant increases in the renal blood flow are scarcely to be expected in cases where two possible sets of factors influencing it remain, and where probably the factor under

investigation is comparatively close to its minimal level under the conditions of the experiment. Lastly, the possibility of sensitization of the denervated renal arterioles to any circulating adrenalin (Rein, 1936) cannot be excluded.

It may be argued that the marked increases in renal blood flow produced by the action of "pyrogenic inulin" (Goldring and Chasis, 1944; Bradley, Chasis, Goldring and Smith, 1945) show that a considerable release of flow may occur in all but the cases with the most advanced renal functional impairment. The mechanism behind these surprisingly large changes in renal circulation seems to be unknown. Those few observations which have been reported tend to show that the response is essentially unchanged after sympathectomy. A blocking of specific factors associated with essential hypertension does not seem the essential principle involved, as the increase in blood flow appears to be proportionally the same in normals.

The repeated observations that there are a rather considerable number of cases of essential hypertension showing filtration rate and effective renal plasma flow entirely within normal limits are confirmed in this study. Whether significant depressions from the levels of the bedrest renal pattern occur during active life, is largely unknown. Studies in which various situations are simulated seem badly needed. The present series is believed to have some value as a scale of reference for the changes to be expected at different levels of reduced renal function.

Even assuming it could be proved that every transitory blood pressure rise involved a significant decrease in renal blood flow, there is as yet no evidence that repeated transitory reductions of renal blood flow may produce persistent hypertension. On the other hand, the failures to produce persistent hypertension by Goldblatt and associates (1941) by means of intermittent partial constriction of the renal artery, or by Kottke, Kubicek and Visscher (1945) with chronic renal artery-nerve stimulation, cannot reasonably be directly transferred from these rather shortlasting animal experiments to the problem of essential hypertension in man.

A thorough analysis of the possible rôle of the renal nerves in essential hypertension should appropriately take into consideration at least the following aspects.

1. A study of the renal hemodynamic pattern during exercise, emotional stress and various other situations before and after sympathectomy.
2. The general tendency to a decline in renal function during the time necessary for such a study in a control material of unoperated hypertensives (about 1—3 years) should be investigated in order to establish a background for the appraisal of the sympathectomized cases.
3. The difficulty of appraising the effect of a blood pressure drop on the renal circulation makes it desirable to carry out the study at a blood

pressure that approaches the preoperative level as closely as possible. To exclude a renal vasoconstrictor action a neurogenic vasoconstrictor agent, *e. g.* CO_2 , should be used for this purpose.

4. To minimize the possible influence of renal arteriolosclerosis the subjects should preferably be below 45 years of age and present no or only moderate extrarenal vascular disease and not too advanced a reduction of renal function. On the other hand, the reduction in renal function must be definite enough to furnish clear evidence of any release that might occur after sympathectomy.

5. A reliable method of ascertaining whether renal denervation has been complete as a result of the sympathectomy seems highly desirable. As already mentioned, Rein and his associates used CO_2 for this purpose in their study of the denervated dog's kidney.

6. An approach to the problem of the intrarenal distribution of the blood flow should preferably be made at the same time.

Summary.

A limited series of young adults in whom definite renal disease had been clinically excluded showed average values for clearances of inulin and diodrast closely comparable to those reported in the literature.

The majority of the cases of essential hypertension showed a decreased effective renal plasma flow with a relatively less decreased filtration rate, leading to a high filtration fraction.

A small number of the cases of essential hypertension showed values above the normal mean.

Classified according to the amount of extrarenal vascular disease, cases with the more advanced lesions exhibited more severely impaired renal function.

A small series of observations (9) in sympathectomized subjects showed a mean filtration fraction within normal limits.

Carbon dioxide inhalation, which in various species of animals has been demonstrated to exert a powerful vasoconstrictor action on the renal circulation, gave the following results.

In normals CO_2 produced a decrease of both C_m and C_b , averaging 19 and 23 per cent respectively.

In cases of essential hypertension and a variety of other kidney disorders with slight to moderate reduction of renal function, the same tendency to decrease of clearances was noted, although somewhat less pronounced. Increasing with the degree of reduction of renal function there was a tendency to abolished or inverted response to CO_2 , some cases showing

definite increases of both clearances. This was noted in cases of essential hypertension and chronic glomerulonephritis with hypertension.

Irrespective of the characteristics of the hypertensive process, higher age has been shown to favour the occurrence of abolished or inverted responses to CO_2 in essential hypertension.

The same tendency, though not so pronounced, was seen when a classification based on the amount of extrarenal vascular disease was undertaken.

In the series of sympathectomized subjects there was an insignificant reduction in the average C_D and a moderate increase in the average C_M due to CO_2 . This response differed somewhat from the one presented by unoperated-upon cases of essential hypertension at the same level of renal function. Under the action of CO_2 three subjects examined before and after sympathectomy showed exactly the same average blood pressure and C_M before and after operation, while the average C_D showed a small increase postoperatively.

Various possible explanations of the changes brought about by CO_2 are discussed. Among them the most plausible one is that CO_2 exerts a vasoconstrictor influence on both sets of renal glomerular arterioles. The abolished and inverted responses to CO_2 occurring in cases with severe reduction of renal function have been thought to be explained by increased resistance of the wall of predominantly the afferent arteriole to the vasoconstrictor action of CO_2 , this being due to advanced arteriosclerotic changes, the increased blood pressure exerting its influence on the renal circulation.

The possible rôle of the renal nerves in essential hypertension has been discussed. The conclusion arrived at is that in the majority of cases the failure to prove a release of the renal circulation after sympathectomy is of very limited value for the exclusion of tonic or, to an even lesser extent, intermittent neurogenic influence on the renal circulation.

Some postulates for a more searching analysis on the effect of sympathectomy on the renal circulation have been outlined.

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